

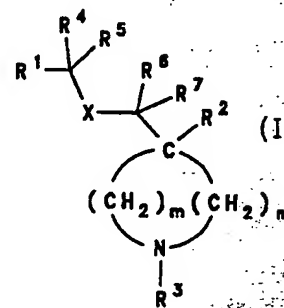


INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁵ : C07D 401/06, 211/22, 211/20 C07D 207/08, 413/06, 417/06 C07D 521/00, A61K 31/445	A1	(11) International Publication Number: WO 94/10165 (43) International Publication Date: 11 May 1994 (11.05.94)												
(21) International Application Number: PCT/GB93/02214 (22) International Filing Date: 27 October 1993 (27.10.93) (30) Priority data: <table border="0"> <tr> <td>9222633.1</td> <td>28 October 1992 (28.10.92)</td> <td>GB</td> </tr> <tr> <td>9308962.1</td> <td>30 April 1993 (30.04.93)</td> <td>GB</td> </tr> <tr> <td>9313680.2</td> <td>2 July 1993 (02.07.93)</td> <td>GB</td> </tr> <tr> <td>9316112.3</td> <td>4 August 1993 (04.08.93)</td> <td>GB</td> </tr> </table> (71) Applicant (for all designated States except US): MERCK SHARP & DOHME LIMITED [GB/GB]; Hertford Road, Hoddesdon, Hertfordshire EN11 9BU (GB). (72) Inventors; and (75) Inventors/Applicants (for US only): HARRISON, Timothy [GB/GB]; 11 Normansfield, Great Dunmow, Essex CM6 1XA (GB). MACLEOD, Angus, Murray [GB/GB]; 24 Abbotts Way, Thorley Park, Bishops Stortford, Hertfordshire CM23 4YE (GB). STEVENSON, Graeme, Irvine [GB/GB]; Ridgemean, Thaxted Road, Debden, Saffron Walden, Essex CB11 3LW (GB). WILLIAMS, Brian, John [GB/GB]; 73 Godfrey Way, Great Dunmow, Essex CM6 2SE (GB).		9222633.1	28 October 1992 (28.10.92)	GB	9308962.1	30 April 1993 (30.04.93)	GB	9313680.2	2 July 1993 (02.07.93)	GB	9316112.3	4 August 1993 (04.08.93)	GB	(74) Agent: COLE, William, Gwyn; Merck & Co., Inc., Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB). (81) Designated States: AU, CA, JP, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report.</i>
9222633.1	28 October 1992 (28.10.92)	GB												
9308962.1	30 April 1993 (30.04.93)	GB												
9313680.2	2 July 1993 (02.07.93)	GB												
9316112.3	4 August 1993 (04.08.93)	GB												

(54) Title: 4-ARYLMETHYLOXYMETHYL PIPERIDINES AS TACHYKININ ANTAGONISTS**(57) Abstract**

Compounds of formula (I) wherein m is 2, 3 or 4; n is 0, 1 or 2 when m is 2 or 3, and n is 0 or 1 when m is 4; X represents O or S; R¹ represents phenyl optionally substituted by 1, 2 or 3 groups selected from C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, halo, cyano, nitro, trifluoromethyl, trimethylsilyl, -OR^a, SR^a, SO₂R^a, -NR^aR^b, -NR^aCOR^b, -NR^aCO₂R^b, -CO₂R^a or -CONR^aR^b, where R^a and R^b each independently represent H, C₁₋₆alkyl, phenyl or trifluoromethyl; R² represents phenyl optionally substituted by 1, 2 or 3 groups selected from C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, halo, cyano, nitro, trifluoromethyl, trimethylsilyl, -OR^a, SR^a, SO₂R^a, -NR^aR^b, -NR^aCOR^b, -NR^aCO₂R^b, -CO₂R^a or -CONR^aR^b, where R^a and R^b are as previously defined; heteroaryl selected from indazolyl, thienyl, furyl, pyridyl, thiazolyl, tetrazolyl and quinolyl; benzhydryl; or benzyl; wherein each heteroaryl and each phenyl moiety of benzyl and benzhydryl may be substituted by C₁₋₆alkyl, C₁₋₆alkoxy, halo or trifluoromethyl; and R³ represents H, COR⁹, CO₂R¹⁰, COCONR¹⁰R¹¹, COCO₂R¹⁰, SO₂R¹⁵, CONR¹⁰SO₂R¹⁵, C₁₋₆alkyl optionally substituted by a group selected from (CO₂R¹⁰, CONR¹⁰R¹¹, hydroxy, cyano, COR⁹, NR¹⁰R¹¹, C(NO₂)NR¹⁰R¹¹, CONHphenyl(C₁₋₄alkyl), COCO₂R¹⁰, COCONR¹⁰R¹¹, SO₂R¹⁵, CONR¹⁰SO₂R¹⁵ and phenyl optionally substituted by one or more substituents selected from C₁₋₆alkyl, C₁₋₆alkoxy, halo and trifluoromethyl), Y-R⁸ or CO-Z-(CH₂)_q-R¹²; R⁴, R⁵, R⁶ and R⁷ each independently represent H or C₁₋₆alkyl; R⁸ represents an optionally substituted aromatic heterocycle; R⁹ represents H, C₁₋₆alkyl or phenyl; R¹⁰ and R¹¹ each independently represent H or C₁₋₆alkyl; R¹² represents NR¹³R¹⁴ or an optionally substituted aromatic or non-aromatic azacyclic or azabicyclic group; R¹³ and R¹⁴ each independently represent H, C₁₋₆alkyl, phenyl optionally substituted by one or more of C₁₋₆alkyl, C₁₋₆alkoxy, halo or trifluoromethyl or phenylC₁₋₄alkyl optionally substituted in the phenyl ring by one or more of C₁₋₆alkyl, C₁₋₆alkoxy, halo or trifluoromethyl; R¹⁵ represents C₁₋₆alkyl, trifluoromethyl or phenyl optionally substituted by one or more substituents selected from C₁₋₆alkyl, C₁₋₆alkoxy, halo and trifluoromethyl; Y represents a hydrocarbon chain of 1, 2, 3 or 4 carbon atoms which may optionally be substituted by oxo; Z represents CH₂, O, S or NR¹⁰; and q represents 0, 1, 2, 3, 4, 5 or 6 and their salts are useful as tachykinin antagonists.



BEST AVAILABLE COPY

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	GB	United Kingdom	MR	Mauritania
AU	Australia	GE	Georgia	MW	Malawi
BB	Barbados	GN	Guinea	NE	Niger
BE	Belgium	GR	Greece	NL	Netherlands
BF	Burkina Faso	HU	Hungary	NO	Norway
BG	Bulgaria	IE	Ireland	NZ	New Zealand
BJ	Benin	IT	Italy	PL	Poland
BR	Brazil	JP	Japan	PT	Portugal
BY	Belarus	KE	Kenya	RO	Romania
CA	Canada	KG	Kyrgyzstan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo	KR	Republic of Korea	SE	Sweden
CH	Switzerland	KZ	Kazakhstan	SI	Slovenia
CI	Côte d'Ivoire	LI	Liechtenstein	SK	Slovakia
CM	Cameroon	LK	Sri Lanka	SN	Senegal
CN	China	LU	Luxembourg	TD	Chad
CS	Czechoslovakia	LV	Latvia	TG	Togo
CZ	Czech Republic	MC	Monaco	TJ	Tajikistan
DE	Germany	MD	Republic of Moldova	TT	Trinidad and Tobago
DK	Denmark	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	US	United States of America
FI	Finland	MN	Mongolia	UZ	Uzbekistan
FR	France			VN	Viet Nam
GA	Gabon				

- 1 -

4-ARYLMETHYLOXYMETHYL PIPERIDINES AS TACHYKININ ANTAGONISTS

5 This invention relates to a class of azacyclic compounds, which are useful as tachykinin antagonists. More particularly, the compounds of the invention comprise an azacyclic ring system substituted by an arylmethoxy or arylmethylthio moiety.

10 The tachykinins are a group of naturally-occurring peptides found widely distributed throughout mammalian tissues, both within the central nervous system and in the peripheral nervous and circulatory systems. The structures of three known mammalian tachykinins are as follows:

15 Substance P:

Arg-Pro-Lys-Pro-Gln-Gln-Phe-Phe-Gly-Leu-Met-NH₂

Neurokinin A:

His-Lys-Thr-Asp-Ser-Phe-Val-Gly-Leu-Met-NH₂

Neurokinin B:

20 Asp-Met-His-Asp-Phe-Phe-Val-Gly-Leu-Met-NH₂

Evidence for the usefulness of tachykinin receptor antagonists in pain, headache, especially migraine, Alzheimer's disease, multiple sclerosis, attenuation of morphine withdrawal, cardiovascular changes, oedema, such as oedema caused by thermal injury, 25 chronic inflammatory diseases such as rheumatoid arthritis, asthma/bronchial hyperreactivity and other respiratory diseases including allergic rhinitis, inflammatory diseases of the gut including ulcerative colitis and Crohn's disease, ocular injury and ocular 30 inflammatory diseases, proliferative vitreoretinopathy, irritable bowel syndrome and disorders of bladder function including cystitis and bladder detrusor hyper-reflexia is reviewed in "Tachykinin Receptors and

- 2 -

Tachykinin Receptor Antagonists", C.A. Maggi, R. Patacchini, P. Rovero and A. Giachetti, J. Auton. Pharmacol. (1993) 13, 23-93. Tachykinin antagonists are also believed to be useful in allergic conditions

5 [Hamelet et al Can. J. Pharmacol. Physiol. (1988) 66 1361-7], immunoregulation [Lotz et al Science (1988) 241 1218-21 and Kimball et al, J. Immunol. (1988) 141 (10) 3564-9], and as anticonvulsants [Garant et al., Brain Research (1986) 382 372-8]. Tachykinin antagonists may

10 also be useful in the treatment of small cell carcinomas, in particular small cell lung cancer (SCLC) [Langdon et al., Cancer Research (1992) 52, 4554-7].

It has furthermore been suggested that tachykinins have utility in the following disorders:

15 depression, dysthymic disorders, chronic obstructive airways disease, hypersensitivity disorders such as poison ivy, vasospastic diseases such as angina and Reynauld's disease, fibrosing and collagen diseases such as scleroderma and eosinophillic fascioliasis, reflex

20 sympathetic dystrophy such as shoulder/hand syndrome, addiction disorders such as alcoholism, stress related somatic disorders, neuropathy, neuralgia, disorders related to immune enhancement or suppression such as systemic lupus erythmatosis (European patent application

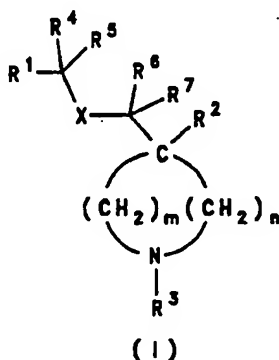
25 no. 0 436 334), conjunctivitis, vernal conjunctivitis, contact dermatitis, atropic dermatitis, urticaria, and other eczematoid dermatitis (European patent application no. 0 394 989) and emesis (European patent application no. 0 533 280).

30 In view of their metabolic instability, peptide derivatives are likely to be of limited utility as therapeutic agents. It is for this reason that non-peptide tachykinin antagonists are sought.

- 3 -

In essence, this invention provides a class of potent non-peptide tachykinin antagonists.

The present invention provides a compound of formula (I), or a salt or prodrug thereof:



wherein

15

m is 2, 3 or 4;

n is 0, 1 or 2 when m is 2 or 3, and n is 0 or 1 when m is 4;

X represents O or S;

20

R¹ represents phenyl optionally substituted by 1, 2 or 3 groups selected from C₁-6alkyl, C₂-6 alkenyl, C₂-6alkynyl, halo, cyano, nitro, trifluoromethyl, trimethylsilyl, -OR^a, SR^a, SOR^a, SO₂R^a, -NR^aR^b, -NR^aCOR^b, -NR^aCO₂R^b, -CO₂R^a or -CONR^aR^b, where R^a and R^b each independently represent H, C₁-6alkyl, phenyl or trifluoromethyl;

25

R² represents phenyl optionally substituted by 1, 2 or 3 groups selected from C₁-6alkyl, C₂-6 alkenyl, C₂-6alkynyl, halo, cyano, nitro, trifluoromethyl, trimethylsilyl, -OR^a, SR^a, SOR^a, SO₂R^a, -NR^aR^b, -NR^aCOR^b, -NR^aCO₂R^b, -CO₂R^a or -CONR^aR^b, where R^a and R^b are as previously defined; heteroaryl selected from indazolyl, thienyl, furyl, pyridyl, thiazolyl, tetrazolyl and quinolyl; benzhydryl; or benzyl; wherein each heteroaryl and each phenyl moiety of benzyl and benzhydryl may be

30

- 4 -

substituted by C₁₋₆alkyl, C₁₋₆alkoxy, halo or trifluoromethyl; and

5 R³ represents H, COR⁹, CO₂R¹⁰, COCONR¹⁰R¹¹, COCO₂R¹⁰, SO₂R¹⁵, CONR¹⁰SO₂R¹⁵, C₁₋₆alkyl optionally substituted by a group selected from (CO₂R¹⁰, CONR¹⁰R¹¹, hydroxy, cyano, COR⁹, NR¹⁰R¹¹, C(NOH)NR¹⁰R¹¹, CONHphenyl(C₁₋₄alkyl), COCO₂R¹⁰, COCONR¹⁰R¹¹, SO₂R¹⁵, CONR¹⁰SO₂R¹⁵ and phenyl optionally substituted by one or more substituents selected from C₁₋₆alkyl, C₁₋₆alkoxy, halo and trifluoromethyl), Y-R⁸ or CO-Z-(CH₂)_q-R¹²;

10 R⁴, R⁵, R⁶ and R⁷ each independently represent H or C₁₋₆alkyl;

R⁸ represents an optionally substituted aromatic heterocycle;

15 R⁹ represents H, C₁₋₆alkyl or phenyl;

R¹⁰ and R¹¹ each independently represent H or C₁₋₆alkyl;

20 R¹² represents NR¹³R¹⁴ or an optionally substituted aromatic or non-aromatic azacyclic or azabicyclic group;

25 R¹³ and R¹⁴ each independently represent H, C₁₋₆alkyl, phenyl optionally substituted by one or more of C₁₋₆alkyl, C₁₋₆alkoxy, halo or trifluoromethyl or phenylC₁₋₄alkyl optionally substituted in the phenyl ring by one or more of C₁₋₆alkyl, C₁₋₆alkoxy, halo or trifluoromethyl;

30 R¹⁵ represents C₁₋₆alkyl, trifluoromethyl or phenyl optionally substituted by one or more substituents selected from C₁₋₆alkyl, C₁₋₆alkoxy, halo and trifluoromethyl;

Y represents a hydrocarbon chain of 1,2,3 or 4 carbon atoms which may optionally be substituted by oxo;

Z represents CH₂, O, S or NR¹⁰; and

q represents 0, 1, 2, 3, 4, 5 or 6.

- 5 -

As used herein, the definition of each expression, when it occurs more than once in any structure, is intended to be independent of its definition elsewhere in the same structure.

5 The alkyl, alkenyl and alkynyl groups referred to with respect to the formulae herein may represent straight, branched or cyclic groups, or combinations thereof. Thus, for example, suitable alkyl groups include methyl, ethyl, n- or iso-propyl, n-, sec-, iso-
10 or tert-butyl, cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, and cycloalkyl-alkyl groups such as cyclopropylmethyl; suitable alkenyl groups include vinyl and allyl; and suitable alkynyl groups include propargyl.

15 The term "halo" as used herein includes fluoro, chloro, bromo and iodo, especially chloro and fluoro.

 The present invention includes within its scope prodrugs of the compounds of formula (I) above. In general, such prodrugs will be functional derivatives of the compounds of formula (I) which are readily
20 convertible in vivo into the required compound of formula (I). Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985. However, most aptly the
25 present invention provides a compound of formula (I) or a pharmaceutically acceptable salt thereof.

 Those compounds according to the invention which contain one or more chiral centres may exist both as enantiomers and as diastereomers. It is to be
30 understood that all such isomers and mixtures thereof are encompassed within the scope of the present invention.

 Preferably m is 2.

 When m is 2, n is preferably 2. When m is 3 or 4, n is preferably 0.

- 6 -

Preferably X represents O.

Preferably R^1 represents substituted phenyl.

When R^1 is substituted phenyl suitable substituents include nitro, trifluoromethyl, trimethylsilyl, bromo, chloro, fluoro, iodo, cyano, methyl, ethyl, cyclopropyl, t-butyl, vinyl, methoxy, phenoxy, amino and carbonylmethoxy. Preferably R^1 represents phenyl substituted by one or more groups selected from C_{1-6} alkyl such as methyl and t-butyl, halo such as chloro, fluoro and bromo, and trifluoromethyl.

Preferably R^1 represents disubstituted phenyl, in particular 3,5-disubstituted phenyl, for example 3,5-disubstituted phenyl wherein the substituents are selected from C_{1-6} alkyl, halo and trifluoromethyl. More preferably R^1 represents 3,5-bis(trifluoromethyl) phenyl.

Suitable values for the group R^2 include unsubstituted or substituted phenyl, 5-membered heteroaryl such as thienyl, 6-membered heteroaryl such as pyridyl, and benzhydryl.

Preferably R^2 represents unsubstituted or substituted phenyl.

When R^2 represents substituted phenyl a preferred substituent is halo, especially fluoro.

When R^8 represents a substituted aromatic heterocycle, suitable substituents in the heterocyclic ring include one or more of C_{1-6} alkyl, C_{1-6} alkoxy, phenyl, oxo, thioxo, halo, trifluoromethyl, NR^aR^b , NR^aCOR^b , $CONR^aR^b$, CO_2R^a , SR^a , SO_2R^a and CH_2OR^a , where R^a and R^b are as previously defined. Particular examples of suitable substituents include methyl, methoxy, phenyl, oxo, thioxo, bromo, iodo, NH_2 , SCH_3 , $CONH_2$ and cyano. Particularly preferred substituents include oxo and NH_2 .

- 7 -

Suitable values for R^8 include thienyl, furyl, pyrrolyl, pyridyl, pyrazolyl, triazolyl, tetrazolyl, thiazolyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl, oxazolyl, oxadiazolyl, thiadiazolyl, isoxazolyl, quinolyl, isothiazolyl, imidazolyl, benzimidazolyl, benzoxazolyl, benzothiophenyl, benzofuranyl and indolyl, any of which may be substituted.

Preferably R^8 represents a substituted or unsubstituted 5- or 6-membered nitrogen containing aromatic heterocycle such as for example oxazolyl, oxadiazolyl, tetrazolyl, thiazolyl, thiadiazolyl, triazolyl, pyrazinyl, pyridyl, pyrimidinyl, pyridazinyl, imidazolyl or triazinyl. More preferably R^8 represents optionally substituted oxazolyl, oxadiazolyl, imidazolyl, thiadiazolyl, triazolyl, pyrazinyl, pyrimidinyl, pyridazinyl or triazinyl, or tetrazolyl substituted by C_{1-6} alkyl, preferably methyl.

It will be appreciated that, when the heterocyclic moiety R^8 is substituted by an oxo or thioxo substituent, different tautomeric forms are possible so that the substituent may be represented as =O or -OH, or =S or -SH, respectively. For the avoidance of doubt, all such tautomeric forms are embraced by the present invention. Favoured heterocyclic moieties R^8 include 5 membered heterocyclic rings containing 1, 2 or 3 nitrogen atoms substituted by oxo. A particularly favoured such moiety is 1,2,4-triazol-3-one.

When R^{12} represents $NR^{13}R^{14}$, R^{13} and R^{14} are preferably both C_{1-6} alkyl such as methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl or t-butyl. More preferably R^{13} and R^{14} will both represent methyl.

When R^{12} represents an aromatic or non-aromatic azacycle or azabicyclo it may contain one or more

- 8 -

additional heteroatoms selected from O, S and N or groups NR^{16} , where R^{16} is H, C_{1-6} alkyl or phenyl C_{1-4} alkyl, and may be unsubstituted or substituted. Suitable substituents include C_{1-6} alkyl, C_{1-6} alkoxy, oxo, SH, =S, halo, trifluoromethyl, NR^aR^b , NR^aCOR^b , $CONR^aR^b$, CO_2R^a and CH_2OR^a , where R^a and R^b are as previously defined.

When R^{12} represents an aromatic azacycle or azabicyclo, suitable values of R^{12} include imidazolyl, triazolyl, tetrazolyl, oxazolyl, thiazolyl, pyrrolyl, pyrazolyl, pyrazinyl, pyridyl, oxadiazolyl, thiadiazolyl, isoxazolyl, isothiazolyl, benzimidazolyl, benzoxazolyl and indolyl, preferably imidazolyl, such as 2,4-imidazolyl, or pyridyl, more preferably pyridyl such as 4-, 3- or 2-pyridyl.

When R^{12} represents a non-aromatic azacycle or azabicyclo, suitable values of R^{12} include morpholinyl, piperdiny, pyrrolidinyl, piperazinyl, methylpiperazinyl, azanorbornanyl, azabicyclo[2.2.2]octanyl and azabicyclo[3.2.2]nonyl, preferably morpholinyl, methylpiperazinyl, quinuclidinyl (azabicyclo[2.2.2]octanyl) or azabicyclo[3.2.2]nonyl, more preferably quinuclidinyl.

Suitably Y represents a hydrocarbon chain of 1 or 2 carbon atoms optionally substituted by oxo, such as CH_2 , $C=O$, $CH(CH_3)$, $CH_2(C=O)$ or $(C=O)CH_2$. Preferably Y represents CH_2 , $CH(CH_3)$ or $CH_2(C=O)$, more preferably CH_2 or $CH(CH_3)$.

Suitably q represents 0, 1, 2 or 3.

Suitable values of R^3 include H, COR^9 such as $COCH_3$, SO_2R^{15} such as SO_2CH_3 , C_{1-6} alkyl such as CH_3 , $CH(CH_3)_2$, $CH_2CH(CH_3)_2$ and $CH_2CH_2C(CH_3)_3$, C_{1-6} alkyl substituted by CO_2R^{10} such as $CH_2CO_2CH_3$, CH_2CO_2H , $(CH_2)_3CO_2CH_3$ and $(CH_2)_3CO_2H$, C_{1-6} alkyl substituted by $CONR^{10}SO_2R^{15}$ such as $CH_2CONHSO_2CH_3$ and $CH_2CONHSO_2C_6H_5$,

- 9 -

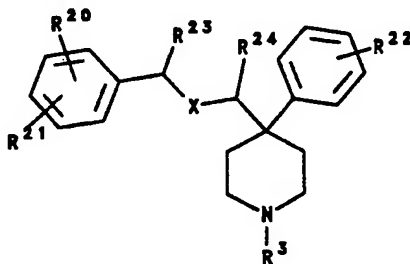
C₁₋₆alkyl substituted by phenyl, Y-R⁸ and CO-Z-(CH₂)_q-R¹². Aptly R⁴, R⁵, R and R⁷ independently represent H or methyl. More aptly R⁴, R⁵ and R⁶ represent H.

5 In one preferred subgroup of compounds according to the invention, R³ represents H or C₁₋₆alkyl, more preferably H.

In a further preferred subgroup of compounds according to the invention R³ represents Y-R⁸.

10 A yet further preferred subgroup of compounds according to the invention is represented by compounds wherein R³ is CO-Z-(CH₂)_q-R¹².

A particular sub-class of compounds according to the invention is represented by compounds of formula
15 (Ia), and salts and prodrugs thereof:



(Ia)

25 wherein

R³ and X are as defined for formula (I);

R²⁰ and R²¹ independently represent H,

C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, halo, cyano, nitro, trifluoromethyl, trimethylsilyl, OR^a, SR^a, SOR^a, SO₂R^a,
30 NR^aR^b, NR^aCOR^b, NR^aCO₂R^b, COR^a or CONR^aR^b, where R^a and R^b are as previously defined;

R²² represents H or halo, preferably H or fluoro, for example 4-fluoro; and

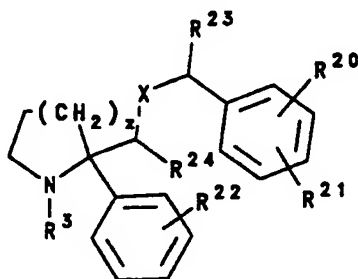
- 10 -

R^{23} and R^{24} each independently represent H or methyl.

Aptly R^{24} represents H. Aptly R^{23} represents methyl.

5 Particular values of R^{20} and R^{21} include H, chloro, bromo, methyl, t-butyl and trifluoromethyl; and also C_{1-6} alkoxy groups such as methoxyl, ethoxyl and isopropoxyl and n, sec- and tert-butoxyl. Preferably R^{20} and R^{21} are both other than H and are located at the 3-
10 and 5-positions of the phenyl ring.

A further sub-class of compounds according to the invention is represented by compounds of formula (Ib), and salts and prodrugs thereof:



(Ib)

wherein R^3 , X, R^{20} , R^{21} , R^{22} , R^{23} and R^{24} are as defined for formula (Ia), above and z is 1 or 2.

25 Specific compounds within the scope of the present invention include:

4-phenyl-4-[(3,5-bistrifluoromethyl)benzyloxy methyl]piperidine;

2-[(3,5-bistrifluoromethyl)benzyloxymethyl]-2-
30 phenylpyrrolidine;

4-phenyl-4-[(2-trifluoromethyl)benzyloxymethyl] piperidine;

4-phenyl-4-benzyloxymethylpiperidine;

- 11 -

- 4-phenyl-4-[(3-chloro-5-t-butyl)benzyloxymethyl]
piperidine;
4-phenyl-4-[(3,5-dichloro)benzyloxymethyl]piperidine;
4-phenyl-4-[(3-trifluoromethyl)benzyloxymethyl]
5 piperidine;
4-phenyl-4-[(4-trifluoromethyl)benzyloxymethyl]
piperidine;
1-acetyl-4-phenyl-4-[(3,5-bistrifluoromethyl)
benzyloxymethyl]piperidine;
10 1-methanesulphonyl-4-phenyl-4-[(3,5-bistrifluoromethyl)
benzyloxymethyl]piperidine;
5-[(4-[(3,5-bistrifluoromethyl)benzyloxymethyl]-4-phenyl-
piperidin-1-ylmethyl)-2,4-dihydro[1,2,4]triazol-3-one;
2-[1'-imidazolyl]acetyl-4-phenyl-4-[(3,5-
15 bistrifluoromethyl)benzyloxymethyl]piperidine;
5-[4-[(3,5-bistrifluoromethyl)benzyloxymethyl]-4-(4-
fluorophenyl)-piperidin-1-ylmethyl]-2,4-
dihydro[1,2,4]triazol-3-one;
5-[4-[(3,5-bistrifluoromethyl)benzyloxymethyl]-4-(2-
20 fluorophenyl)-piperidin-1-yl)methyl]-2,4-
dihydro[1,2,4]triazol-3-one;
5-[4-[(3,5-bistrifluoromethyl)benzyloxymethyl]-4-(3-
fluorophenyl)-piperidin-1-yl)methyl]-2,4-
dihydro[1,2,4]triazol-3-one;
25 3-phenyl-3-[(3,5-bistrifluoromethyl)benzyloxymethyl]
piperidine);
4-phenyl-[4-[1-(3,5-bis(trifluoromethyl)phenyl]
ethoxymethyl]piperidine;
1-methyl-4-phenyl-4-[3,5-bis(trifluoromethyl)
30 benzyloxymethyl]piperidine;
1-isopropyl-4-phenyl-4-[3,5-bis(trifluoromethyl)
benzyloxymethyl]piperidine;
1-(2-phenyl)ethyl-4-phenyl-4-[3,5-bis(trifluoromethyl)
benzyloxymethyl]piperidine;

- 12 -

- 1-isobutyryl-4-phenyl-4-[3,5-bis(trifluoromethyl)benzyloxymethyl]piperidine;
1-isovaleryl-4-phenyl-4-[3,5-bis(trifluoromethyl)benzyloxymethyl]piperidine;
5 (±)-5-[4-[1-(3,5-bis(trifluoromethyl)phenyl)ethoxymethyl]-4-phenyl-piperidin-1-yl]-2,4-dihydro-[1,2,4]triazol-3-one;
4-phenyl-4-[(3-chloro-5-methyl)benzyloxymethyl]piperidine;
10 4-phenyl-4-[(3-bromo-5-methyl)benzyloxymethyl]piperidine;
4-phenyl-4-[(3-methyl-5-t-butyl)benzyloxymethyl]piperidine;
methyl-2-[4-phenyl-4-(3,5-bis(trifluoromethyl)benzyloxymethyl)piperidine]acetate;
15 N-methyl-4-phenyl-4-[3,5-bis(trifluoromethyl)benzyloxymethyl]piperidine;
4-[3,5-bis(trifluoromethyl)benzyloxymethyl]-4-phenyl-1-(4H-[1,2,4]triazol-3-yl-methyl)piperidine;
20 5-[4-(3-methyl-5-t-butyl)benzyloxymethyl]4-phenylpiperidin-1-ylmethyl]2,4-dihydro-[1,2,4]triazol-3-one;
2-[4-phenyl-4-[3,5-bis(trifluoromethyl)benzyloxymethyl]-N-3-pyridylmethyl-N-methylacetamide;
25 4-[3,5-bis(trifluoromethyl)benzyloxymethyl]-1-(2-methylthiazol-5-ylmethyl)-4-phenylpiperidine;
4-[3,5-bis(trifluoromethyl)benzyloxymethyl]-1-[1,2,4]oxadiazol-3-ylmethyl-4-phenylpiperidine;
(±)-5-[4-(3,5-bis(trifluoromethyl)benzyloxymethyl)-4-phenylpiperidinyl-1-ethyl]-2,4-dihydro-[1,2,4]triazol-3-one;
30 1-[4-(3,5-bis(trifluoromethyl)benzyloxymethyl)-4-phenylpiperidin-1-yl]-2-pyrrolidin-1-ylacetamide;

- 13 -

- N-methanesulphonyl-2-[4-phenyl-4-(3,5-bis(trifluoromethyl)benzyloxymethyl)piperidin-1-yl]acetamide;
- 5 N-phenylsulphonyl-2-[4-phenyl-4-(3,5-bis(trifluoromethyl)benzyloxymethyl)piperidin-1-yl]acetamide;
- 4-phenyl-4-[(3-phenyl)benzyloxymethyl]piperidine;
- 5-[4-(3-phenyl)benzyloxymethyl]-4-phenylpiperidin-1-ylmethyl-2,4-dihydro-[1,2,4]triazol-3-one;
- 10 5-[4-(4-benzyloxymethyl)-4-phenyl-piperidin-1-ylmethyl]-2,4-dihydro-[1,2,4]triazol-3-one;
- N-[2-amino-2-methylpropionamido]-4-phenyl-4-[3,5-bis(trifluoromethyl)benzyloxymethyl]piperidine;
- 4-phenyl-4-[3,5-bis(trifluoromethyl)benzyloxyethyl]piperidine;
- 15 4-(3,4-dichlorophenyl)-4-[3,5-bis(trifluoromethyl)benzyloxymethyl]piperidine;
- 1-[4-(3,5-bis(trifluoromethyl)benzyloxymethyl)-4-phenyl-piperidin-1-yl]-2-pyridin-3-ylethanone;
- 20 1-[4-(3,5-bis(trifluoromethyl)benzyloxymethyl)-4-phenyl-piperidin-1-yl]-2-pyridin-2-ylethanone;
- 1-[4-(3,5-bis(trifluoromethyl)benzyloxymethyl)-4-phenyl-piperidin-1-yl]-2-pyridin-4-ylethanone;
- 1-[4-(3,5-bis(trifluoromethyl)benzyloxymethyl)-4-phenyl-piperidin-1-yl]-3-dimethylamino-propan-1-one;
- 25 2-[4-(3,5-bis(trifluoromethyl)benzyloxymethyl)-4-phenyl-piperidin-1-yl]acetate;
- 4-[4-(3,5-bis(trifluoromethyl)benzyloxymethyl)-4-phenyl-piperidin-1-yl]butyrate;
- 30 methyl-4-[4-(3,5-bis(trifluoromethyl)benzyloxymethyl)-4-phenyl-piperidin-1-yl]butyrate;
- 1-[4-(3,5-bis(trifluoromethyl)benzyloxymethyl)-4-phenyl-piperidin-1-yl]-3-dimethylaminoethanone;

- 14 -

- 1-[4-(3,5-bis(trifluoromethyl)benzyloxymethyl)-4-phenyl-piperidin-1-yl]-3-dimethylaminopent-1-one;
4-(3,5-bis(trifluoromethyl)benzyloxymethyl)-1-[1-(4-toluenesulphonyl)-imidazole-2-yl]methyl-4-phenylpiperidine;
5 4-(3,5-bis(trifluoromethyl)benzyloxymethyl)-1-(1H-imidazole-2-yl-methyl)-4-phenyl-piperidine;
5-[4-(1-[3-bromophenyl]-ethoxymethyl)-4-phenyl-piperidin-1-ylmethyl]-2,4-dihydro-[1,2,4]-triazol-3-one;
10 4-phenyl-4-(1-(3-bromophenyl)-ethoxymethyl)-piperidine hydrochloride;
5-[4-(1-[3-chlorophenyl]-ethoxymethyl)-4-phenyl-piperidin-1-ylmethyl]-2,4-dihydro-[1,2,4]-triazol-3-one;
4-phenyl-4-[3-iodobenzyloxymethyl]-ethoxymethyl)-piperidine;
15 5-[4-(3-iodobenzyloxymethyl)-4-phenyl-piperidin-1-ylmethyl]-2,4-dihydro-[1,2,4]-triazol-3-one;
4-phenyl-4-[3-chlorobenzyloxymethyl]-piperidine hydrochloride;
20 5-[4-(3-chlorobenzyloxymethyl)-4-phenyl-piperidin-1-ylmethyl]-2,4-dihydro-[1,2,4]-triazol-3-one;
1-[4-(3,5-dimethoxybenzyloxymethyl)-4-phenyl-piperidin-1-yl]-2-(1H-indole-3-yl) acetamide;
4-[4-(3,5-dimethoxybenzyloxymethyl)-4-phenyl-piperidin-1-ylmethyl]-quinoline;
25 3-[2-[4-(3,5-dimethoxybenzyloxymethyl)-4-phenyl-piperidin-1-yl]ethyl]-1H-indole;
1-(4-[3,5-dichlorophenyl]-ethoxymethyl)-4-phenyl-piperidin-1-yl)-2-pyrrolidin-acetamide hydrochloride;
30 4-phenyl-4-[3-^t-butylbenzyloxymethyl]-piperidine;
4-phenyl-4-[3-cyanobenzyloxymethyl]-piperidine;
5-[4-(3-cyanobenzyloxymethyl)-4-phenyl-piperidin-1-ylmethyl]-2,4-dihydro-[1,2,4]-triazol-3-one;

- 15 -

- 4-phenyl-4-[4-cyanobenzyloxymethyl]-piperidine hydrochloride;
- 5-[4-(4-cyanobenzyloxymethyl)-4-phenyl-piperidin-1-ylmethyl]-2,4-dihydro-[1,2,4]-triazol-3-one;
- 5-[4-(3-^t-butylbenzyloxymethyl)-4-phenyl-piperidin-1-ylmethyl]-2,4-dihydro-[1,2,4]-triazol-3-one;
- 1-[4-(3,5-dimethoxybenzyloxymethyl)-4-phenyl-piperidin-1-yl]-3-piperidin-4-yl-propionamide hydrochloride;
- 1-(4-(3,5-dichlorobenzyloxymethyl)-4-phenyl-piperidin-1-yl)-2-pyrrolidine acetamide hydrochloride;
- 4-[3-chloro-5-methoxybenzyloxymethyl)-4-phenyl-piperidine hydrochloride;
- 5-[4-(3-chloro-5-methoxybenzyloxymethyl)-4-phenyl-piperidin-1-ylmethyl]-2,4-dihydro-[1,2,4]-triazol-3-one;
- 4-[3,5-bis(trifluoromethyl)benzyloxymethyl]-4-phenyl-1-(5-pyrrolodineethyl)carbamate piperidine hydrochloride;
- 5-[4-(3,5-bismethylbenzyloxymethyl)-4-phenyl-piperidin-1-ylmethyl]-2,4-dihydro-[1,2,4]-triazol-3-one;
- (±)-5-[4-(1-(3-N,N-dimethylphenyl)-ethoxymethyl)-4-phenyl-piperidin-1-ylmethyl]-2,4-dihydro-[1,2,4]-triazol-3-one;
- 4-phenyl-4-[1-(3-isopropoxy)benzyloxymethyl]piperidine hydrochloride;
- 5-[4-(1-(3-isopropoxyphenyl)-ethoxymethyl)-4-phenyl-piperidin-1-ylmethyl]-2,4-dihydro-[1,2,4]-triazol-3-one;
- 4-phenyl-4-(2-cyanobenzyloxymethyl)piperidine hydrochloride;
- 4-(4-methoxyphenyl)-4-[(3,5-bis(trifluoromethyl)benzyloxymethyl)piperidine hydrochloride;
- 4-phenyl-4-[(2-methoxy-5-bromo)benzyloxymethyl]piperidine hydrochloride;
- 4-phenyl-4-[1-(3,6-dichlorophenyl)-ethoxymethyl]piperidine hydrochloride;

- 16 -

4-phenyl-4-[1-(2,3-dichlorophenyl)-ethoxymethyl]piperidine hydrochloride;
4-phenyl-4-[2,3-(dimethoxy)benzyloxymethyl]piperidine hydrochloride;

- 5 5-[4-(3-isopropoxy)benzyloxymethyl-4-phenyl-piperidin-1-ylmethyl]2,4-dihydro-[1,2,4]-triazol-3-one;
4-[3-(trifluoromethoxy)benzyloxymethyl]-4-phenyl-piperidine hydrochloride;
(+)5-[4-(1-[3-bromophenyl]-ethoxymethyl)-4-phenyl-piperidin-1-ylmethyl]-2,4-dihydro-[1,2,4]-triazol-3-one;
10 (-)5-[4-(1-[3-bromophenyl]-ethoxymethyl)-4-phenyl-piperidin-1-ylmethyl]-2,4-dihydro-[1,2,4]-triazol-3-one;
and salts thereof; and more especially the pharmaceutically acceptable salts thereof.

- 15 For use in medicine, the salts of the compounds of formula (I) will be pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of the compounds according to the invention (such as the dibenzoyltartrate salts) or of their pharmaceutically
20 acceptable salts. Suitable pharmaceutically acceptable salts of the compounds of this invention include acid addition salts which may, for example, be formed by mixing a solution of the compound according to the invention with a solution of a pharmaceutically
25 acceptable non-toxic acid such as hydrochloric acid, sulphuric acid, fumaric acid, maleic acid, succinic acid, acetic acid, citric acid, tartaric acid, carbonic acid, phosphoric acid or p-toluenesulphonic acid. Salts of amine groups may also comprise quaternary ammonium salts
30 in which the amino nitrogen atom carries a suitable organic group such as an alkyl, alkenyl, alkynyl or aralkyl moiety. Furthermore, where the compounds of the invention carry an acidic moiety, suitable pharmaceutically acceptable salts thereof may include

- 17 -

metal salts such as alkali metal salts, e.g. sodium or potassium salts; and alkaline earth metal salts, e.g. calcium or magnesium salts.

5 Favoured salts of the compounds according to the invention are acid addition salts of pharmaceutically acceptable acids.

Preferred salts of the compounds according to the invention include the hydrochloride and p-toluenesulphonic acid salts.

10 The invention also provides pharmaceutical compositions comprising one or more compounds of this invention in association with a pharmaceutically acceptable carrier. Preferably these compositions are in unit dosage forms such as tablets, pills, capsules,
15 powders, granules, solutions or suspensions, or suppositories, for oral, parenteral or rectal administration, or topical administration including administration by inhalation or insufflation.

The invention further provides a process for
20 the preparation of a pharmaceutical composition comprising a compound of formula (I), or a salt or prodrug thereof, and a pharmaceutically acceptable carrier, which process comprises bringing a compound of formula (I), or a salt or prodrug thereof into
25 association with a pharmaceutically acceptable carrier.

For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g. conventional tableting ingredients such as corn starch, lactose,
30 sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, e.g. water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention, or a non-

- 18 -

toxic pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of the active ingredient of the present invention, for example 1 to 100 mg. The tablets or pills of the novel composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous solutions, suitably flavoured syrups, aqueous or oil suspensions, and flavoured emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium

- 19 -

carboxymethylcellulose, methylcellulose, polyvinylpyrrolidone or gelatin.

5 Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as set out above. Preferably the compositions are administered by the oral or nasal respiratory route
10 for local or systemic effect. Compositions in preferably sterile pharmaceutically acceptable solvents may be nebulised by use of inert gases. Nebulised solutions may be breathed directly from the nebulising device or the nebulising device may be attached to a face mask, tent or
15 intermittent positive pressure breathing machine. Solution, suspension or powder compositions may be administered, preferably orally or nasally, from devices which deliver the formulation in an appropriate manner.

For topical administration, for example as a
20 cream, ointment or lotion, pharmaceutically acceptable carriers are, for example, water, mixtures of water and water-miscible solvents such as lower alkanols or arylalkanols, vegetable oils, polyalkylene glycols, petroleum based jelly, ethyl cellulose, ethyl oleate,
25 carboxymethylcellulose, polyvinylpyrrolidone, isopropyl myristate and other conventionally-employed non-toxic, pharmaceutically acceptable organic and inorganic carriers. The pharmaceutical preparation may also contain non-toxic auxiliary substances such as
30 emulsifying, preserving, wetting agents, bodying agents and the like, as for example, polyethylene glycols 200, 300, 400 and 600, carbowaxes 1,000, 1,500, 4,000, 6,000 and 10,000, antibacterial components such as quaternary ammonium compounds, phenylmercuric salts known to have

- 20 -

cold sterilizing properties and which are non-injurious in use, thimerosal, methyl and propyl paraben, benzyl alcohol, phenyl ethanol, buffering ingredients such as sodium chloride, sodium borate, sodium acetates, gluconate buffers, and other conventional ingredients such as sorbitan monolaurate, triethanolamine, oleate, polyoxyethylene sorbitan monopalmitate, dioctyl sodium sulfosuccinate, monothioglycerol, thiosorbitol, ethylenediamine tetraacetic acid, and the like.

The present invention further provides a process for the preparation of a pharmaceutical composition comprising a compound of formula (I), which process comprises bringing a compound of formula (I) into association with a pharmaceutically acceptable carrier or excipient.

The compounds of formula (I) are of value in the treatment of a wide variety of clinical conditions which are characterised by the presence of an excess of tachykinin, in particular substance P, activity. These may include disorders of the central nervous system such as anxiety, depression, psychosis and schizophrenia; epilepsy; neurodegenerative disorders such as dementia, including senile dementia of the Alzheimer type, Alzheimer's disease and Down's syndrome; demyelinating diseases such as MS and ALS and other neuropathological disorders such as peripheral neuropathy, including diabetic and chemotherapy-induced neuropathy, and postherpetic and other neuralgias; small cell carcinomas such as small cell lung cancer; respiratory diseases, particularly those associated with excess mucus secretion such as chronic obstructive airways disease, bronchopneumonia, chronic bronchitis, cystic fibrosis and asthma, and bronchospasm; inflammatory diseases such as inflammatory bowel disease, psoriasis, fibrositis,

- 21 -

osteoarthritis and rheumatoid arthritis; allergies such as eczema and rhinitis; hypersensitivity disorders such as poison ivy; ophthalmic diseases such as conjunctivitis, vernal conjunctivitis, and the like; 5 cutaneous diseases such as contact dermatitis, atropic dermatitis, urticaria, and other eczematoid dermatitis; addiction disorders such as alcoholism; stress related somatic disorders; reflex sympathetic dystrophy such as shoulder/hand syndrome; dysthymic disorders; adverse 10 immunological reactions such as rejection of transplanted tissues and disorders related to immune enhancement or suppression such as systemic lupus erythematosus; gastrointestinal (GI) disorders and diseases of the GI tract such as disorders associated with the neuronal 15 control of viscera such as ulcerative colitis, Crohn's disease and incontinence; emesis, including acute, delayed and anticipatory emesis, for example, induced by chemotherapy, radiation, toxins, pregnancy, vestibular disorders, surgery, migraine and variations in 20 intercranial pressure; disorders of bladder function such as bladder detrusor hyper-reflexia; fibrosing and collagen diseases such as scleroderma and eosinophilic fascioliasis; disorders of blood flow caused by vasodilation and vasospastic diseases such as angina, 25 migraine and Reynaud's disease; and pain or nociception, for example, that attributable to or associated with any of the foregoing conditions, especially the transmission of pain in migraine, visceral pain and post operative pain.

30 The compounds of formula (I) are particularly useful in the treatment of pain or nociception and/or inflammation and disorders associated therewith such as, for example, neuropathy, such as diabetic and chemotherapy-induced neuropathy, postherpetic and other

- 22 -

neuralgias, asthma, osteoarthritis, rheumatoid arthritis and especially migraine and post operative pain.

The compounds of the formula (I) are useful in treating more than one symptom at a time, for example
5 emesis and pain following surgery.

The present invention further provides a compound of formula (I), or a salt or prodrug thereof, for use in therapy.

According to a further or alternative aspect,
10 the present invention provides a compound of formula (I) or a pharmaceutically acceptable salt thereof for use in the manufacture of a medicament for the treatment of physiological disorders associated with an excess of tachykinins, especially substance P.

15 The present invention also provides a method for the treatment or prevention of physiological disorders associated with an excess of tachykinins, especially substance P, which method comprises administration to a patient in need thereof of a
20 tachykinin reducing amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof or a composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof.

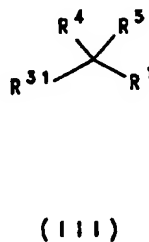
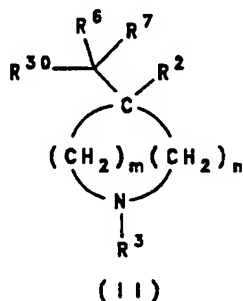
For the treatment of certain conditions it may
25 be desirable to employ a compound according to the present invention in conjunction with another pharmacologically active agent. For example, for the treatment of respiratory diseases such as asthma, a compound of formula (I) may be used in conjunction with a
30 bronchodilator, such as a β_2 -adrenergic receptor antagonist or tachykinin antagonist which acts at NK-2 receptors. The compound of formula (I) and the bronchodilator may be administered to a patient simultaneously, sequentially or in combination.

5

10

15

25



- 24 -

wherein R^1 , R^2 , R^4 , R^5 , R^6 , R^7 , m and n are as defined for formula (I), R^3 is as defined for formula (I) except that, when R^3 is H it is replaced by a suitable protecting group, such as $CO_2(C_{1-6}alkyl)$; and one of R^{30} and R^{31} represents a leaving group and the other of R^{30} and R^{31} represents XH, where X is as defined for formula (I); in the presence of a base, followed by deprotection, if required.

Suitably R^{30} represents XH and R^{31} represents a leaving group.

Suitable leaving groups include halo, e.g. chloro, bromo or iodo, or sulphonate derivatives such as tosylate or mesylate.

The reaction is conveniently carried out in a suitable organic solvent, such as an ether, e.g. 1,2-dimethoxyethane, at a temperature in the region of $0^\circ C$. Favoured bases of use in the reaction include alkali metal amides and hydrides, such as potassium bis(trimethylsilyl)amide or potassium hydride. Suitably, potassium bis(trimethylsilyl)amide is used.

Compounds of formula (I) may also be prepared from different compounds of formula (I) by interconversion processes. In particular, interconversion processes may be used to vary the group R^3 . For example, compounds of formula (I) wherein R^3 is other than H may be prepared from the corresponding compounds of formula (I) wherein R^3 is H by conventional methods, such as reaction with a compound R^3-Hal , where Hal represents halo, in the presence of a base. Suitable reagents and conditions will be readily apparent to those skilled in the art and are illustrated by the accompanying Examples. It will be appreciated therefore that compounds of the formula (I) wherein R^3 is H are highly favoured compounds of this invention since in

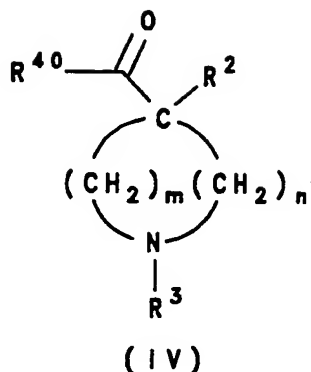
- 25 -

addition to possessing useful biological activity they are of use as intermediates. Suitable bases include organic bases, such as tertiary amines, e.g. triethylamine, and inorganic bases, such as alkali metal carbonates, e.g. sodium carbonate. Compounds of formula (I) wherein R^3 is COR^9 may also be prepared from compounds of formula (I) wherein R^3 is H by, for example, reaction with an appropriate acid anhydride. Compounds of formula (I) wherein R^3 is C_{1-6} alkyl may be prepared from corresponding compounds of formula (I) wherein R^3 is COR^9 by reduction using, for example, borane or a borohydride such as sodium cyanoborohydride. Suitable procedures will be readily apparent to those skilled in the art. Compounds of formula (I) wherein R^3 is C_{1-6} alkyl substituted by $CONR^{10}R^{11}$ may be prepared from corresponding compounds of formula (I) wherein R^3 is C_{1-6} alkyl substituted by CO_2R^{10} by treatment with ammonia or an amine of formula $NR^{10}R^{11}$.

The intermediates of formula (II) above wherein R^{30} is SH may be prepared from the corresponding intermediates of formula (II) wherein R^{30} represents OH by treating the latter compound with Lawesson's reagent or phosphorus pentasulphide in a suitable solvent, e.g. pyridine, at ambient or elevated temperatures, suitably at reflux temperature.

Intermediates of formula (II) above wherein R^{30} is OH and R^6 and R^7 both represent H may be prepared from corresponding compounds of formula (IV):

- 26 -



wherein R^2 , R^3 , m and n are as defined for formula (II) above and R^{40} represents hydroxy, alkoxy or amino, by reduction. Suitable reducing agents will be readily apparent to one skilled in the art and include, for example, metallic hydrides, such as lithium aluminium hydride.

Intermediates of formula (II) wherein R^{30} is OH and one of R^6 and R^7 is C_{1-6} alkyl and the other of R^6 and R^7 is H may be prepared from compounds of formula (IV) wherein R^{40} is H, by reaction with a Grignard reagent of formula $MgHalR^6$ or $MgHalR^7$, wherein R^6 and R^7 are as previously defined and Hal is halo such as chloro, bromo or iodo. Intermediates of formula (II) wherein R^{30} is OH and both of R^6 and R^7 represent C_{1-6} alkyl may be prepared from compounds of formula (IV) wherein R^{40} is alkoxy by reaction with Grignard reagents of formulae $MgHalR^6$ and $MgHalR^7$, as above defined. Suitable reaction conditions will be readily apparent to those skilled in the art.

Compounds of formula (IV) wherein R^{40} is H may be prepared from compounds of formula (IV) wherein R^{40} is alkoxy or amino by reduction. Suitable reducing agents will be readily apparent to those skilled in the art and include, for example, where R^{40} is alkoxy,

- 27 -

diisobutylaluminium hydride, and, where R^{40} is amino, lithium aluminium hydride.

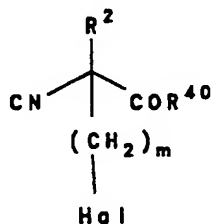
Intermediates of formula (II) wherein R^{30} is a leaving group may be prepared from compounds of formula (II) wherein R^{30} is OH, for example, by reaction with a thionyl halide, a mesyl halide or a tosyl halide.

Where they are not commercially available, the intermediates of formula (III) above may be prepared by the procedures described in the accompanying Examples or by alternative procedures which will be readily apparent to one skilled in the art.

Compounds of formula (IV) are commercially available, or may be prepared by known procedures.

For example, suitable methods for the preparation of compounds of formula (IV) are described in European Patent Application no. 0 337 167, J. Am. Chem. Soc., 81, 1201 (1959), J. Med. Chem., 17, 453 (1974) and J. Med. Chem., 24, 218 (1981).

In general, compounds of formula (IV) wherein R^3 is H, R^{40} is alkoxy and n is 0 may be prepared by cyclisation of an intermediate of formula (V)



(V)

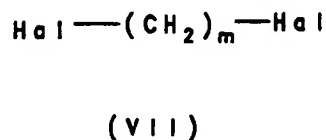
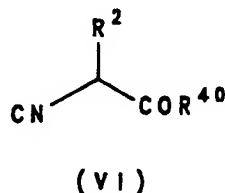
wherein R^2 , R^{40} and m are as previously defined, and Hal represents halo, for example, chloro or bromo, in the presence of a base.

Suitable bases of use in the reaction include tertiary amines, such as, for example, triethylamine.

- 28 -

The reaction is conveniently effected in a suitable organic solvent, such as an ether, for example, tetrahydrofuran, suitably at elevated temperature, such as the reflux temperature of the chosen solvent.

- 5 Intermediates of formula (V) may be prepared by reaction of compounds of formula (VI) with compounds of formula (VII)



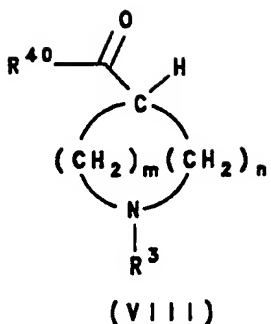
wherein R^2 , R^{40} , m and Hal are as previously defined, in the presence of a base.

- 20 Suitable bases of use in the reaction include alkali metal hydrides, such as, for example, sodium hydride. The reaction is conveniently effected in a suitable organic solvent, such as an ether, for example, tetrahydrofuran, suitably at elevated temperature, such as the reflux temperature of the chosen solvent.

- 25 Compounds of formulae (VI) and (VII) are commercially available, or may be prepared from commercially available starting materials using conventional procedures well known to those skilled in the art.

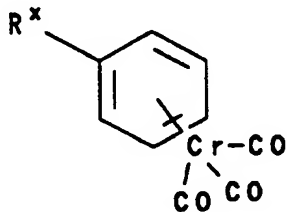
- 30 Compounds of formula (IV) wherein R^{40} is alkoxy and n is other than 0 may in general be prepared from the corresponding compounds of formula (VIII)

- 29 -



10 wherein R^3 , R^{40} and m are as previously defined and n is 1 or 2 by treatment with a base and reaction of the resulting nucleophile with a reagent suitable to introduce the group R^2 , such as an activated aryl moiety, for example

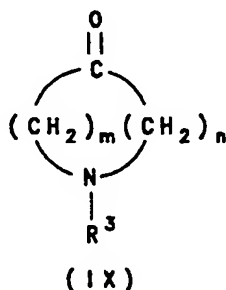
15



wherein R^x is H or halo, such as chloro; an aryl iodide in the presence of nickel bromide (J. Am. Chem. Soc., 99, 4833 (1977)); or a hypervalent aryl iodide (Synthesis, 709 (1984)).

25

Compounds of formula (VIII) may be prepared from the corresponding intermediates of formula (IX)



- 30 -

wherein R^3 , m and n are as defined for formula (VIII) by conventional methods, for example, by sequential reaction with 1,3-dithiane and an alcohol of formula $R^{40}H$, where R^{40} is alkoxy, in the presence of an acid, such as a
5 mineral acid, for example, hydrochloric acid.

Still further procedures suitable for the preparation of compounds of formula (IV) will be readily apparent to those skilled in the art.

Compounds of the formula (I) wherein R^4 is a
10 C_{1-6} alkyl group and R^5 is hydrogen may be prepared by reduction or a corresponding compound of the formula (I) wherein R^4 and R^5 together with the carbon to which that are attached represent a $C=C(R^{41})R^{51}$ group wherein R^{41} and R^{51} are independently hydrogen or alkyl of 1 to 5
15 carbon atoms. Such compounds of formula (I) may be prepared from the corresponding compound of formula (I) wherein R^4 is hydrogen and R^5 is hydrogen by the method of P. Kocienski and M. Mortimore, T. Lett., 29 (27), 3375-3360, 1988. More suitably R^{41} is hydrogen. More
20 suitably R^{51} is hydrogen. Most suitably this process is adapted to the preparation of a compound of the formula (I) wherein R^4 is methyl and R^5 is hydrogen.

Where the above-described process for the preparation of the compounds according to the invention
25 gives rise to mixtures of stereoisomers these isomers may, if desired, be separated, suitably by conventional techniques such as preparative chromatography.

The novel compounds which contain one or more chiral centres may be prepared in racemic form, or
30 individual enantiomers may be prepared either by enantiospecific synthesis or by resolution. For example, intermediate alcohols of formula (II), wherein R^{30} is OH, may be resolved into their component enantiomers by standard techniques, such as the formation of

- 31 -

diastereomeric esters or amides, followed by chromatographic separation or separation by fractional crystallization and removal of the chiral auxiliary. The diastereomeric alcohols can then be used to prepare optically pure compounds of formula (I).

During any of the above synthetic sequences it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in Protective Groups in Organic Chemistry, ed. J.F.W. McOmie, Plenum Press, 1973; and T.W. Greene and P.G.M. Wuts, Protective Groups in Organic Synthesis, John Wiley & Sons, 1991. The protecting groups may be removed at a convenient subsequent stage using methods known from the art.

Using test methods described in PCT/GB92/01212 (International Publication No. WO 93/01159) pages 30-33, it was found that the compounds referred to in the Examples hereinafter had IC₅₀ at NKIR of less than 500 nM.

The following illustrate pharmaceutical compositions according to the invention.

Tablets containing 1-25mg of compound

	<u>Amount mg</u>		
Compound of formula (I)	1.0	2.0	25.0
Microcrystalline cellulose	20.0	20.0	20.0
Modified food corn starch	20.0	20.0	20.0
Lactose	58.5	57.5	34.5
Magnesium Stearate	0.5	0.5	0.5

Tablets containing 26-100mg of compound

	<u>Amount mg</u>		
Compound of formula (I)	26.0	50.0	100.0

- 32 -

Microcrystalline cellulose	80.0	80.0	80.0
Modified food corn starch	80.0	80.0	80.0
Lactose	213.5	189.5	139.5
Magnesium Stearate	0.5	0.5	0.5

- 5 The compound of formula (I), cellulose, lactose and a portion of the corn starch are mixed and granulated with 10% corn starch paste. The resulting granulation is sieved, dried and blended with the remainder of the corn starch and the magnesium stearate. The resulting
- 10 granulation is then compressed into tablets containing 1.0mg, 2.0mg, 25.0mg, 26.0mg, 50.0mg and 100mg of the active compound per tablet.

Parenteral injection

15		<u>Amount mg</u>
	Compound of formula (I)	1 to 100mg
	Citric Acid Monohydrate	0.75mg
	Sodium Phosphate	4.5mg
	Sodium Chloride	9mg

- 20 Water for Injections to 1ml

The sodium phosphate, citric acid monohydrate and sodium chloride are dissolved in a portion of the water. The compound of formula (I) is dissolved or suspended in the solution and made up to volume.

25

Topical formulation

		<u>Amount mg</u>
	Compound of formula (I)	1-10g
	Emulsifying Wax	30g
30	Liquid paraffin	20g
	White Soft Paraffin	to 100g

The white soft paraffin is heated until molten. The liquid paraffin and emulsifying wax are incorporated and stirred until dissolved. The compound of formula (I) is

- 33 -

added and stirring continued until dispersed. The mixture is then cooled until solid.

The following Examples illustrate the preparation of compounds according to the invention.

EXAMPLE 11-t-Butoxycarbonyl-4-phenyl-4-[(3,5-bis(trifluoromethyl)benzyloxymethyl)piperidine]

5 a) 4-Phenyl-4-carboxy piperidine tosylate (10g) was added portionwise to a solution of lithium aluminium hydride (1.52g) in dry tetrahydrofuran (100ml) at 0°C. After addition was complete the reaction mixture was warmed to reflux for 30 min and then allowed to cool to room temperature. The reaction was then quenched by addition of 2N sodium hydroxide solution until a white granular precipitate formed. The mixture was filtered and the filtrate 10 extracted with ethyl acetate (200ml), dried (MgSO₄), filtered and solvent removed to afford a clear oil. The residual oil was taken up in dichloromethane (50ml) and di-t-butyl-dicarbonate (1.9g) added. The resulting mixture was stirred at room temperature for 18h. Solvent 15 removed and the residual oil subjected to flash chromatography on silica gel to afford 1-t-butoxycarbonyl-4-phenyl-4-hydroxymethyl piperidine as a colourless oil (2.1g). ¹H NMR (360MHz, CDCl₃) 1.43 (9H, s, C(CH₃)₃), 1.75 (2H, td, J = 11.0, 10Hz, NCH₂CH₂), 2.17 (2H, m, NCH₂), 3.05 (2H, td, J = 11.0, 1.0Hz, NCH₂CH₂), 3.55 (2H, s, CH₂-OH), 3.73 (2H, m, NCH₂), 7.24-7.41 (5H, m, ArH); m/z (CI⁺) 292 (M⁺+1).

25 b) Sodium hydride (120mg x 60%) was added to a stirred solution of 1-t-butoxycarbonyl-4-phenyl-4-hydroxymethyl piperidine (760mg), and 3,5-bis(trifluoromethyl)benzylbromide (801mg), in dry dimethylformamide (5ml). The resulting solution was stirred for 18 hours at room temperature, poured into water (100ml) and extracted into ethyl acetate (50ml). The organic extract was washed with water (3 x 50ml), brine (2 x 50ml), dried (MgSO₄), filtered and the solvent 30 removed to afford a yellow oil. Purification by flash chromatography on silica gel using 15% ethyl acetate/n hexane as eluant, afforded 1-t-butoxycarbonyl-4-phenyl-4-[(3,5-bis(trifluoromethyl)benzyl

-35-

oxymethyl]piperidine as a clear oil (900mg). ^1H NMR (360MHz, CDCl_3) 1.46 (9H, s, $\text{C}(\text{CH}_3)_3$), 1.86 (2H, td, $J = 10.0, 1.0\text{Hz}$, $\text{NCH}_2\text{CHH} \times 2$), 2.21 (2H, m, HHCNCHH), 3.03 (2H, td, $J = 10.0, 1.0\text{Hz}$, $\text{NCH}_2\text{CHH} \times 2$), 3.45 (2H, s, $\text{CH}_2\text{-O-CH}_2\text{Ar}$), 3.76 (2H, m, HHCNCHH), 4.43 (2H, s, $\text{CH}_2\text{-OCH}_2\text{Ar}$), 7.24 (2H, m, $\text{ArH} \times 2$), 7.33 (3H, m, $\text{ArH} \times 3$), 7.54 (2H, s, $\text{C-CH-CCF}_3 \times 2$), 7.73 (1H, s, $\text{CF}_3\text{-C-CH-CCF}_3$); m/z (CI^+) 518 (M^++1).

EXAMPLE 2

4-Phenyl-4-[(3,5-bistrifluoromethyl)benzyloxymethyl]piperidine hydrochloride

1- t Butoxycarbonyl-4-phenyl-4-[(3,5-bistrifluoromethyl)benzyloxymethyl] piperidine (900mg) was dissolved in dry diethyl ether and a stream of dry hydrogen chloride gas poured through the solution for 30 mins. The solution was stirred for a further 2.5h at room temperature, at which point the solvent was removed under reduced pressure to afford a white solid. Recrystallisation from ethyl acetate afforded 4-Phenyl-4-[(3,5-Bistrifluoromethyl)benzyloxymethyl] piperidine hydrochloride as a white amorphous solid (260mg); mp $139\text{-}141^\circ\text{C}$. ^1H NMR (250MHz, DMSO-d_6) 2.08 (2H, m, $\text{N-CH}_2\text{CHH} \times 2$), 2.19 (2H, m, HHC-NCHH), 2.73 (2H, m, $\text{NCH}_2\text{-CHH} \times 2$), 3.21 (2H, m, HHC-N-CHH), 3.49 (2H, s, $\text{CH}_2\text{-OCH}_2\text{Ar}$), 4.58 (2H, s, $\text{CH}_2\text{-OCH}_2\text{Ar}$), 7.27 (5H, m, ArH), 7.77 (2H, $\text{C-CH-CF}_3 \times 2$), 7.98 (1H, s, $\text{CF}_3\text{-C-CH-CCF}_3$); m/z (CI^+) (M^++1). $\text{C}_{21}\text{H}_{21}\text{NOF}_6\cdot\text{HCl}$ requires C, 55.57; H, 4.88; N, 3.08 Found C, 55.39; H, 4.88; N, 3.13%.

EXAMPLE 3

2-[(3,5-Bis-trifluoromethyl)benzyl]oxymethyl-2-phenyl pyrrolidine

a) Lithium aluminium hydride (1M in tetrahydrofuran; 10.6ml) was added to a cooled (0°C) suspension of (±)-2-phenylproline hydrochloride (0.85g) and the mixture heated at reflux for 1.5h. After cooling to 0°C, water (1ml) was added followed by 2M NaOH (1ml) and water (2ml). The reaction mixture was diluted with ethyl acetate (50ml) then filtered through a pad of Hi-flo and the residue concentrated in vacuo to give (±)-2-phenylprolinol as a yellow oil which solidified on standing. ¹H NMR (250MHz, CDCl₃) δ 7.42-7.20 (5H, m, ArH), 3.60 (1H, d, J = 10.0Hz, CHHOH), 3.49 (1H, d, J = 10.0Hz, CHHOH), 3.07 (2H, t, J = 5.7Hz, CH₂N), 2.43 (2H, br s, OH and NH), 2.19-1.75 (4H, m).

b) A solution of 2-phenylprolinol (0.51g) and di-t-butylidicarbonate (0.66g) in dichloromethane (4ml) was stirred at 23°C for 16h. Evaporation of the solvent in vacuo provided 1-t-butyloxycarbonyl-2-phenylprolinol as an oil. ¹H NMR (360MHz, CDCl₃) δ 7.36-7.17 (5H, m, ArH), 5.27 (1H, d, J = 7.2Hz, CHHOH), 4.27 (1H, t, J = 7.6Hz), 3.94 (1H, d, J = 7.2Hz, CHHOH), 3.66 (1H, s, J = 7.4Hz), 3.51 (1H, m), 1.94 (2H, m), 1.8-1.66 (2H, m), 1.50 (9H, s). ¹³C NMR (90.6MHz, CDCl₃) δ 156.3, 141.9, 128.3, 126.6, 126.0, 80.4, 71.8, 66.9, 49.1, 40.1, 28.5, 20.9.

c) Sodium hydride (80% in oil, 52mg) was added to a solution of 1-t-butyloxycarbonyl-2-phenylprolinol (370mg) and 3,5-bis-(trifluoromethyl)benzyl bromide (0.366ml) in dry N,N-dimethylformamide (1ml) and the mixture was stirred at 23°C for 18h. Water (20ml) was added and the mixture extracted with ethyl acetate (3 x 20ml). The combined organic phases were washed with brine (1 x 10ml) then dried (MgSO₄) and concentrated to leave a yellow oil. Purification by chromatography on silica gel using hexane-ethyl acetate (19:1 then 9:1 then 4:1) as eluant provided 1-t-butyloxycarbonyl-2-((3,5-bis-trifluoromethyl)benzyloxymethyl)-2-phenyl pyrrolidine as a white solid. ¹H NMR (250MHz, CDCl₃) δ 7.84

-37-

(3H, app d), 7.26 (5H, m), 4.70 (2H, d, $J = 8.4\text{Hz}$), 4.38 (0.5H, d, $J = 9.8\text{Hz}$), 4.18 (0.5H, d, $J = 8.4\text{Hz}$), 4.12 (0.5H, d, $J = 8.4\text{Hz}$), 3.97 (0.5H, d, $J = 9.8\text{Hz}$), 3.85-3.44 (2H, m), 2.57 (1H, m), 2.06 (1H, m), 1.94-1.56 (2H, m), 1.43 (5H, s), 1.14 (4H, s).

5

d) A solution of the product of part c) (0.1g) in trifluoroacetic acid (2ml) was stirred at 23°C for 10min. Excess solvent was removed in vacuo and the residue partitioned between dichloromethane and 2M sodium hydroxide solution. The layers were separated, and the aqueous phase extracted once with dichloromethane. The combined organic phases were dried (K_2CO_3) and concentrated to leave a colourless, viscous oil. The HCl salt was prepared (HCl in methanol and recrystallised from hexane-ether, to give 2-((3,5-bis-trifluoromethyl)-benzyloxymethyl)-2-phenyl pyrrolidine hydrochloride salt, mp = $152-155^{\circ}\text{C}$. ^1H NMR (360MHz, CD_3OD) δ 7.99 (1H, s), 7.68 (2H, s), 7.54-7.37 (5H, m), 4.70 (d, $J = 14\text{Hz}$), 4.62 (d, $J = 14\text{Hz}$), 3.90 (d, $J = 7\text{Hz}$), 3.84 (d, $J = 7\text{Hz}$), 3.38 (2H, m), 2.48 (1H, m), 2.26 (1H, m), 2.10 (1H, m), 1.97 (1H, m). MS (CI^+) m/z 404 (MH, 100%).

10

15

20

The following Examples were prepared following the procedures of Examples 1 and 2.

EXAMPLE 4

25

4-Phenyl-4-(2-trifluoromethyl)benzyloxymethyl piperidine hydrochloride

Mpt = 181°C ; ^1H NMR (360MHz, $\text{DMSO}-d_6$) δ 2.07-2.21 (2H, m), 2.28-2.39 (2H, m), 2.64-2.78 (2H, m), 3.12-3.23 (2H, m), 3.51 (2H, s), 4.53 (2H, s), 7.24-7.72 (9H, m), 9.00 (2H, br). MS, CI^+ , 350 (M^+); $\text{C}_{20}\text{H}_{22}\text{F}_3\text{NO} \cdot \text{HCl}$ requires C, 62.26; H, 6.01; N, 3.63; found C, 61.92, H, 5.97; N, 3.66.

30

EXAMPLE 54-Phenyl-4-benzyloxymethylpiperidine hydrochloride

5 Mpt = 156°C; ¹H NMR (360MHz, DMSO-d₆) δ 2.06-2.18 (2H, m), 2.27-2.39 (2H, m), 2.62-2.76 (2H, m), 3.09-3.21 (2H, m), 3.41 (2H, s), 4.38 (2H, s), 7.13-7.46 (10H, m), 9.05 (2H, br); MS, CI⁺, 282 (M⁺); C₁₉H₂₃NO.HCl.1.8H₂O requires C, 68.31; H, 7.78; N, 4.19; found C, 68.34; H, 7.58; N, 4.23.

EXAMPLE 6

10 4-Phenyl-4-(3-chloro-5-^t-butyl)benzyloxymethylpiperidine
hydrochloride

15 Mpt = 75°C, ¹H NMR (360MHz, DMSO-d₆) δ 1.24 (9H, s), 2.04-2.15 (2H, m), 2.30-2.38 (2H, m), 2.67-2.77 (2H, m), 3.12-3.20 (2H, m), 3.43 (2H, s), 4.40 (2H, s), 6.98 (1H, s), 7.11 (1H, s), 7.24-7.31 (2H, m), 7.36-7.46 (4H, m), 9.02 (2H, br). C₂₃H₃₀ClNO.HCl requires C, 67.74; H, 7.65; N, 3.43 found C, 67.38; H, 7.95; N, 3.26.

EXAMPLE 7

20 4-Phenyl-4-(3,5-dichlorobenzyloxymethyl)piperidine
hydrochloride

25 Mpt = 180°C. ¹H NMR (360MHz, DMSAO-d₆) δ 2.04-2.14 (2H, m), 2.07-2.19 (2H, m), 2.66-2.77 (2H, m), 3.12-3.22 (2H, m), 3.41 (2H, s), 4.40 (2H, s), 7.11 (2H, s), 7.21-7.47 (6H, m); MS (CI⁺), 350, 352 (M⁺); C₁₉H₂₁Cl₂NO. 1.5HCl requires C, 56.35; H, 5.60; N, 3.45. Found C, 56.71; H, 5.49; N, 3.38%.

EXAMPLE 84-Phenyl-4-(3-trifluoromethylbenzyloxymethyl)piperidine hydrochloride

5 Mpt = 194-195°C. ¹H NMR (360MHz, DMSO-d₆) δ 2.06-2.18 (2H, m), 2.30-2.40 (2H, m), 2.66-2.79 (2H, m), 3.11-3.21 (2H, m), 3.46 (2H, s), 4.49 (2H, s), 7.26-7.64 (8H, m) 8.82-9.08 (1H, b), 9.11-9.25 (1H, b); MS, CI⁺, 350 (M⁺). C₂₀H₂₂F₃NO.HCl requires C, 62.226; H, 6.01; N, 3.63. Found C, 62.33; H, 6.08; N, 3.75.

10

EXAMPLE 94-Phenyl-4-(4-trifluoromethylbenzyloxymethyl)piperidine hydrochloride

15 Mpt = 113°C. ¹H NMR (360MHz, DMSO-d₆) δ 2.09-2.20 (2H, m), 2.30-2.42 (2H, m), 2.64-2.80 (2H, m), 3.13-3.22 (2H, m), 3.46 (2H, s), 4.52 (2H, s), 7.26-7.49 (7H, m), 7.61-7.69 (2H, d, J = 8.1Hz), 8.96-9.06 (1H, b), 9.15-9.21 (1H, b); MS, CI⁺, 350 (M⁺ +1). C₂₀H₂₂F₃NO.1.5HCl.H₂O requires C, 56.91; H, 6.09; N, 3.32. Found C, 56.79; H, 6.14; N, 3.38.

20

EXAMPLE 101-Acetyl-4-phenyl-4-(3,5-bis(trifluoromethyl) benzyloxymethyl) piperidine

25 Acetyl chloride (86mg) was added to a stirred solution of the compound of Example 2 (500mg) and triethylamine (310ml) in dry dichloromethane at 0°C. The resulting solution was allowed to warm to room temperature overnight. The reaction mixture was diluted with water (50ml) and the organic layer separated. The aqueous layer was extracted with dichloromethane, and the combined organic extracts washed with 1N sodium hydroxide solution, dried (MgSO₄), filtered and the solvent removed under reduced pressure to afford a

-40-

clear oil. Recrystallisation from hexane/ether afforded the product as white needles. mpt = 64-65°C; ¹H NMR (360MHz, DMSO-d₆) δ 1.70-1.80 (1H, m), 1.81-1.91 (1H, m), 1.97 (3H, s), 2.04-2.22 (2H, br m), 2.90-2.99 (1H, m), 3.09-3.19 (1H, m), 3.51 (2H, s), 3.55-3.63 (1H, m), 3.80-3.89 (1H, m), 4.55 (2H, s), 7.20-7.45 (5H, m), 7.75 (2H, s), 7.96 (1H, s). MS, CI⁺, 460 (M⁺). C₂₃H₂₃F₆NO₂·0.25H₂O requires C, 59.55; H, 5.10; N, 3.02 found C, 59.68; H, 4.88; N, 2.90.

EXAMPLE 11

10 1-Methanesulphonyl-4-phenyl-4-(3,5-bis(trifluoromethyl)benzyloxymethyl) piperidine

The title compound was prepared analogously to the preparation of Example 10: mpt = 102-104°C, ¹H NMR (360MHz, DMSO-d₆) δ 1.97-2.08 (2H, m), 2.36-2.46 (2H, m), 2.66 (3H, s), 2.80-2.90 (2H, m), 3.44 (2H, s), 3.55-3.64 (2H, m), 4.44 (2H, s), 7.24-7.44 (5H, m), 7.52 (2H, s), 7.73 (1H, s). MS, CI⁺, 496 (M⁺), 513 (M+NH₄)⁺. C₂₂H₂₃F₆NO₃S requires C, 53.33; H, 4.68; N, 2.83 found C, 53.06; H, 4.93; N, 2.73.

20

EXAMPLE 12

5-[(4-(3,5-Bis-trifluoromethyl-benzyloxymethyl)-4-phenyl-piperidin-1-yl)methyl]-2,4-dihydro-[1,2,4]-triazol-3-one

a) Sodium methoxide (400mg) was added to a stirred solution of chloroacetonitrile (20g) in dry methanol (120ml). The resulting solution was stirred for 1 hour at room temperature, and then neutralised by the addition of acetic acid. ^tButyl carbazate (35g) was then added and stirring continued for a further 1 hour. The solvent was then removed under reduced pressure and the residue taken up in ethyl acetate, washed with water, the organic layer separated and dried (MgSO₄). Filtration and removal of solvent

gave a white solid. Recrystallisation from isopropanol afforded N-t-Butoxycarbonyl chloromethyl imidrazone as white needles (31g).
mpt = 69-70°C; ¹H NMR (360MHz, CDCl₃) δ 1.24 (9H, s, C(CH₃)₃),
4.00 (2H, s, Cl-CH₂-), 5.6 (2H, bs, NH₂), 8.7 (1H, bs, NH-CO).

5

b) The product of part a) (7.1g) was added to a stirred suspension of the compound of Example 2 (15.0g) in dry DMF (50ml) and the resulting solution stirred for 24 hours at room temperature. The reaction mixture was poured into water and the aqueous mixture extracted into ethyl acetate. The organic extract was washed exhaustively with water, and finally brine, dried (MgSO₄), filtered and the solvent removed to afford a yellow solid. The recovered material was re-dissolved in dry toluene and warmed to reflux for 30 minutes in the presence of a catalytic amount of potassium t-butoxide. The solvent was removed under reduced pressure and the residue purified by chromatography on silica gel (15% EtOAc/nHex) to afford the product as a white powder (17.2g). The recovered product was taken up in dry ether and HCl gas passed through the solution. The product crystallised as a white powder on stirring (18.1g). mp = 159-160°C. ¹H NMR (360MHz, CDCl₃) δ 2.1 (2H, m, NCH₂CHH x 2), 2.23 (2H, m, HHC-NCHH), 2.61 (2H, m, NCH₂CHH x 2), 2.93 (2H, m, HHCNCHH), 3.36 (2H, s, CH₂OCH₂Ar), 3.80 (1H, d, J = 15Hz, NCHH-Met), 4.1 (1H, d, J = 15.0Hz, NCHH-Met), 4.2 (2H, s, CH₂OCH₂ Ar), 7.1-7.25 (5H, m, ArH), 7.76 (2H, s, C-CH-CF₃ x 2); m/z (CI⁺) 515 (M⁺+1). C₂₄H₂₄N₄O₂F₆.HCl.H₂O requires C, 50.66; H, 4.78; N, 9.84 Found C, 50.30; H, 4.49; N, 9.55%.

10

15

20

25

EXAMPLE 13

30

2-[1'-Imidazolyl]acetyl-4-phenyl-4[(3,5-bis(trifluoromethyl)1,1-benzyloxymethyl)piperidine tosylate

a) The compound of Example 2 (1.36g) was stirred with triethylamine (836μl) in anhydrous dichloromethane (70ml) under an

-42-

inert atmosphere for 15 minutes. Bromoacetyl bromide (382 μ l) was added by syringe in one portion and the reaction mixture stirred for 2.5 hours at room temperature. The solution was washed sequentially with 40ml aliquots of 2N HCl, 0.4M NaHCO₃ and water, dried (MgSO₄) and evaporated to a brown gum (1.8g). The recovered material was purified by flash silica gel chromatography in ethyl acetate/petrol (2:3) to afford a colourless oil, 1.0g. ¹H NMR (360MHz, CDCl₃) δ 7.74 (1H, s, A-H Ar), 7.54 (2H, s, 2-H and 6-H Ar), 7.36-7.42 (4H, m) and 7.27-7.31 (1H, m, Ph), 4.45 (2H, s, OCH₂ Ar), 4.22 (1H, dt, J = 13.7 and < 3Hz, CHHNCHH), 4.05 and 3.85 (2H total, 2 x 2, COCH₂Br), 3.69 (1H, dt, J = 13.6 and < 3Hz, CHHNCHH), 3.46 (2H, s, CH₂OBr), 3.27 (1H, dt, J = 12.5 and 2.7Hz, CHHCHH), 2.98 (1H, dt, J = 12.5 and 3.0Hz, CHHNCHH), 2.26-2.43 (2H, bm, CHH.C.CHH), 1.85-2.04 (2H, m, CHH.C.CHH). m/z (CI⁺) 538, 540 (M+1, 1:1, 45%), 460 (M-Br + 2H, 100%).

b) The compound of step a) (225mg) was stirred with sodium imidazole (45mg) in anhydrous dimethylsulphoxide (2.5ml) under an inert atmosphere for 2 hours at 60°C. The cooled solution was diluted with water (10ml) and extracted with ethyl acetate (4 x 10ml). The combined organic extracts were washed once with a saturated brine solution (10ml), dried (Na₂SO₄) and evaporated to dryness (180mg). The crude residue was purified by flash silica gel chromatography in dichloromethane-methanol (18:1) to yield the title compound as its free base (85mg). Treatment with one equivalent of pTSA in ether afforded the title compound as a white powder. mp 197.5-199.5°C. ¹H NMR (360MHz, d₆-DMSO) δ 8.95 (1H, s, H-2 imid.), 7.98 (1H, s, 4-H Ar), 7.76 (2H, s, 2-H and 6-H Ar), 7.63 and 7.58 (2 x 1H, 2 x d, J < 3Hz, H-4 and H-5 imid.), 7.45-7.49 (4H, m, 2H(Ph) and 2H(Tol)), 7.37 (2H, t, J = 7.6Hz, 2H Ph), 7.25 (1H, t, J = 7.2Hz, 4-H Ph), 7.10 (2H, d, J = 7.7Hz, 2H Tol), 5.36 (1H, d, J = 16.6Hz) and 5.23 (1H, d, J = 16.6Hz, OCH₂Ar), 4.57 (2H, s, COCH₂N), 3.85 (1H, dt, J = 13.4 and < 4Hz) and 3.56 (1H, dt, J = 13.4 and < 3Hz, CHHNCHH), 3.32 (2H, s,

-43-

CH₂OBr), 3.20 (1H, bt, J = 10.4Hz) and 3.04 (1H, bt J = 10.3Hz, CHHNCHH), 2.28 (3H, s, CH₃), 2.15-2.30 (2H, bm, CHH.C.CHH), 1.97 (1H, bt, J = 10.2Hz) and 1.83 (1H, bt, J = 10.1Hz, CHH.C.CHH). m/z (CI⁺) 526 (M+1, 72%) 298 (76%). C₂₆H₂₅F₆N₃O₂.C₇H₈O₃S requires: C, 56.81; H, 4.77; N, 6.02; Found C, 56.99; H, 4.50; N, 5.87%.

EXAMPLE 14

5-[4-(3,5-Bistrifluoromethylbenzyloxymethyl)-4-(4-fluorophenyl)-piperidin-1-ylmethyl]-2,4-dihydro[1,2,4]-triazol-3-one

10 a) 4-Fluorophenyl acetic acid (25g) was dissolved in anhydrous methanol, stirred under nitrogen and cooled in an ice/methanol bath. Dry HCl gas was bubbled through the reaction for 1 hr. The methanol was removed by rotary evaporator, the residue was dispersed between aqueous sodium hydrogen carbonate and
15 dichloromethane. The organic layer was washed with brine, dried (MgSO₄) and concentrated to afford a clear oil (24.4g). ¹H NMR (360MHz, CDCl₃) δ_H 3.61 (2H, s, CH₂), 3.70 (3H, s, CH₃), 6.97-7.06 (2H, m, ArH), 7.20-7.27 (2H, m, ArH). MS m/z CI⁺ 169 (M+1⁺, 100%).

20 b) The 4-fluorophenyl methyl acetate (24.4g) was dissolved in dry dimethyl sulphoxide (150ml) and added via a dropping funnel to sodium hydride (80% wt 15.7g) under nitrogen. After the slow addition was complete the dianion was left to form over a period of 20 mins. Mechlorethamine hydrochloride (24g) was dissolved in dry
25 dimethyl sulphoxide (125ml) and placed in a dropping funnel and added to the dianion over a period of 20 mins. The reaction was poured onto ice (2 dm³) and left overnight. The aqueous mixture was extracted with diethyl ether (50 x 250ml), the combined organics were acidified with 5N HCl (1 dm³). The aqueous layer was basified using
30 potassium carbonate and extracted with ethyl acetate (3 x 250ml). The combined organics were dried (MgSO₄) and concentrated *in vacuo* to afford a brown oil. The oil was purified by flash chromatography

eluted with 100% EtOAc graduated to 8% methanol in ethyl acetate, to afford the product as a light brown oil (9.5g). ^1H NMR (360MHz, CDCl_3) δ_{H} 1.9-2.03 (2H, m, NCH_2CH_2), 2.07-2.19 (2H, m, NCH_2CH_2), 2.27 (3H, s, NCH_3), 2.51-2.62 (2H, m, NCH_2), 2.72-2.86 (2H, m, NCH_2), 3.65 (3H, s, OOCH_3), 6.98-7.06 (2H, m, ArH), 7.27-7.39 (2H, m, ArH). MS CI^+ m/z 224 ($\text{M}+1^+$, 100%).

c) The ester (7.13g) was dissolved in anhydrous THF (40ml) and stirred under nitrogen. Lithium aluminium hydride (1.0M in tetrahydrofuran 14.2ml) was added and the reaction was left stirring at room temperature for 1 hour. Water (0.54ml) followed by 15% NaOH (0.54ml) and finally more water (1.6ml) were added. The reaction was diluted down with tetrahydrofuran and filtered through celite. The solvent was removed to afford a white solid (5.94g). ^1H NMR (360MHz, CDCl_3) δ_{H} 1.84-1.95 (2H, m, NCH_2CH_2), 2.12-2.24 (7H, m, $\text{CH}_3 + \text{NCH}_2\text{CH}_2$), 2.51-2.59 (2H, m, NCH_2), 3.55 (2H, s, CH_2O), 7.02-7.09 (2H, m, ArH), 7.23-7.34 (2H, m, ArH). MS CI^+ m/z 224 ($\text{M}+1^+$, 100%).

d) The alcohol (4.1g) was dissolved in anhydrous dimethyl formamide (60ml), sodium hydride (0.61g) was added portionwise and the reaction sonicated for 30 minutes. The 3,5-bis(trifluoromethyl) benzyl bromide (3.5ml) was added, the colour changed from light brown to almost black and back to light brown, heat was evolved. The reaction was left for 3 hrs. The reaction mixture was dispersed between water/ethyl acetate. The aqueous layer was extracted with ethyl acetate (2 x 50ml). The combined organics were washed with brine, dried (MgSO_4) and concentrated to afford a brown oil. Purification was carried out on flash silica elution 1% methanol in dichloromethane \rightarrow 6% methanol in dichloromethane which afforded a light brown oil (4.2g). ^1H NMR (360MHz, CDCl_3) δ_{H} 1.98-2.12 (2H, m, NCH_2CH_2), 2.18-2.35 (7H, m, $\text{CH}_3 + \text{NCH}_2\text{CH}_2$), 2.58-2.76 (2H, m, NCH_2), 3.44 (2H, s, CH_2O), 4.44 (2H, s, $\text{CH}_2\text{OCH}_2\text{Ar}$), 7.00-7.08 (2H,

-45-

m, ArH), 7.53 (2H, s, ortho H), 7.74 (1H, s, para H). MS Cl^+ m/z 450 ($M^+ + 1$, 100%).

5 e) The alkylated product (4.18g) was dissolved in 1,2 dichloroethane (40ml) under nitrogen, vinyl chloroformate (2.4ml) was added and the reaction was heated at reflux for 18 hrs. An extra portion of vinyl chloroformate (1ml) was added and a further 2 hrs of heating at reflux was required for complete reaction. The 1,2 dichloroethane was removed by rotary evaporator. Purification was carried out on flash silica elution 100%. Dichloromethane to afford a light brown oil (3.1g). ^1H NMR (360MHz, CDCl_3) δ_{H} 1.85-1.93 (2H, m, NCH_2CH_2), 2.22-2.31 (2H, m, NCH_2CH_2), 3.43 (2H, s, OCH_2C), 3.86-3.92 (2H, m, NCH_2), 4.42-4.50 (3H, m, $\text{OCH}_2\text{Ar} + =\text{CHH}$), 4.74-4.79 (1H, dd, $=\text{CHH}$), 7.03-7.11 (2H, m, ortho H [fluorine ring]), 7.17-7.23 (1H, m, $-\text{CH}=\text{CH}_2$), 7.29-7.36 (2H, m, meta ArH), 7.53 (2H, s, ortho CF_3H), 7.75 (1H, s, para H's). MS Cl^+ m/z 506 ($M^+ + 1$, 30%) 523 ($M + (\text{NH}_4)^+$, 70%).

20 f) The vinyl oxycarbonyl group was removed by stirring in methanolic hydrogen chloride solution for 3 hrs. When the reaction is complete by TLC the methanol is removed *in vacuo* to afford the hydrochloride salt as a white solid. Without further purification the hydrochloride salt (1.8g) was dissolved in dimethylformamide (15ml) under nitrogen, an excess of potassium carbonate (2.63g) and the N-t-butoxychloromethylimidiazole (0.95g) were added and stirred at room temperature overnight. When no starting material remained by TLC (10% MeOH in DCM), the reaction mixture was dispersed between water and ethyl acetate. The aqueous layer was extracted with ethyl acetate (2 x 30ml). The combined organics were washed with brine, dried (MgSO_4) and concentrated to afford a brown oil. The recovered oil was dissolved in toluene with a catalytic amount of potassium t-butoxide and heated at 80°C for 3 hrs. Purification was carried out on flash silica eluted with 4% MeOH in DCM rising to 8% MeOH in

DCM. Further purification on Lobar column elution with 5% MeOH in DCM to afford a white solid (0.65g). Recrystallisation was carried out from diethyl ether/hexane. ^1H NMR (360MHz, CDCl_3) δ_{H} 1.95-2.06 (2H, m, NCH_2CH_2), 2.19-2.39 (4H, m, NCH_2CH_2), 2.62-2.72 (2H, m, NCH_2), 3.35 (2H, s, NCH_2 het), 3.44 (2H, s, CCH_2O), 4.43 (2H, s, OCH_2Ar), 7.00-7.07 (2H, t, $J_1 = 8.6\text{Hz}$, $J_2 = 8.7\text{Hz}$, meta H), 7.26-7.32 (2H, dd, $J = 8.8\text{Hz}$, $J = 5.2\text{Hz}$, ortho H's), 7.51 (2H, s, ortho H), 7.73 (1H, s, para H). MS CI^+ m/z 533 ($\text{M}^+ + 1$, 100%). $\text{C}_{24}\text{H}_{23}\text{N}_4\text{O}_2\text{F}_7$ requires C, 54.14; H, 4.35; N, 0.52 found C, 54.16; H, 4.20; N, 10.23.

EXAMPLE 15

5-[4-(3,5-Bistrifluoromethylbenzyloxymethyl)-4-(2-fluorophenyl)-piperidin-1-ylmethyl]-2,4-dihydro-[1,2,4]-triazol-3-one

Prepared analogously to Example 14. Mp 107-110°C. ^1H NMR (360MHz, CDCl_3) δ_{H} 10.4 (~1H, bs, NH), 7.71 (1H, s, 4'-H Ar'), 7.47 (2H, s, 2'-H and 6'-H Ar'), 7.21-7.31 (2H, m, 4-H and 6-H Ar), 7.12 (1H, t, $J = 6.9\text{Hz}$, 5-H Ar), 6.90 (1H, dd, $J_{\text{H-F}} = 13.3$, $J_{\text{H-H}} = 8.1\text{Hz}$, 3-H Ar), 4.45 (2H, s, $\text{OCH}_2\text{Ar}'$), 3.68 (2H, s, CH_2O), 3.35 (2H, s, NCH_2), 2.6-2.7 (2H, bm), 2.3-2.5 (4H, bm) and 1.95-2.05 (2H, bm, $(\text{CH}_2\text{CH}_2)_2\text{N}$). m/z (CI^+) 533 ($\text{M} + 1$, 100%); (CI^-) 531 ($\text{M} - 1$, 8). Found C, 53.51; H, 4.22; N, 10.02. $\text{C}_{24}\text{H}_{23}\text{F}_7\text{N}_4\text{O}_2 \cdot 0.4\text{H}_2\text{O}$ requires C, 53.42; H, 4.45; N, 10.38.

EXAMPLE 16

5-[4-(3,5-Bistrifluoromethylbenzyloxymethyl)-4-(3-fluorophenyl)-piperidin-1-ylmethyl]-2,4-dihydro-[1,2,4]-triazol-3-one

Prepared analogously to Example 14. ^1H NMR (360MHz, CDCl_3) δ_{H} 1.96-2.02 (2H, m, NCH_2CH_2), 2.20-2.24 (2H, m, NCH_2CH_2), 2.30-2.38 (2H, m, NCH_2), 2.64-2.70 (2H, m, NCH_2), 3.34 (2H, s, NCH_2 het), 3.46 (2H, s, CCH_2O), 4.44 (2H, s, OCH_2Ar), 6.92-

-47-

6.97 (H, m, ArH), 7.03-7.06 (1H, m, ArH), 7.10-7.19 (1H, m, ArH), 7.28-7.34 (H, m, ArH), 7.61 (2H, s, ArH), 7.73 (1H, s, ArH), 10.14 (1H, bs, NH). MS CI^+ m/z 533 ($\text{M}+1^+$, 40%). mp 107-108°C.

5

EXAMPLE 17**3-Phenyl-3-(3,5-bistrifluoromethyl)benzyloxymethyl piperidine tosylate****a) 4-Phenyl, 4,4-diethoxycarbonyl butyronitrile**

10

15

20

25

Acrylonitrile (33.0g) was added dropwise to a stirred solution of diethyl phenylmalonate (70.8g) in dry t-Butanol (80ml). After the addition of approximately 20 drops, a solution of 30% methanolic potassium hydroxide (1.0ml) was added. Once the addition of acrylonitrile was complete, further 30% methanolic potassium hydroxide (1.0ml) was added and the reaction warmed to 50°C for one hour. The reaction mixture was allowed to cool to room temperature, then diluted with water (250ml) and extracted into ether. The organic extract was dried (MgSO_4), filtered, and the solvent removed under reduced pressure. The recovered product was purified by distillation (75g). bp 159-162°C @ 1.2mmHg. ^1H NMR (360MHz, CDCl_3) δ_{H} 1.26 (6H, t, $J=7.5\text{Hz}$, $2 \times \text{CH}_2\text{CH}_3$), 2.34 (2H, t, $J=4.0\text{Hz}$, $\text{CH}_2\text{CH}_2\text{CH}$), 2.62 (2H, t, $J=4.0\text{Hz}$, $\text{CH}_2\text{CH}_2\text{CH}$), 4.26 (4H, m, $2 \times \text{CH}_2\text{CH}_3$), 7.34 (5H, m, Ar H); m/z (CI^+) 307 ($\text{M} + \text{NH}_4^+$) $^+$.

b) 3-Phenyl-3-ethoxycarbonyl piperidine 2-one

30

A solution of 4-phenyl 4,4 diethoxycarbonyl butyronitrile (16.49g) in dry ethanol (250ml) was hydrogenated over platinum dioxide at 50psi for 8 hours. The catalyst was filtered off and the solvent removed under reduced pressure. Product recrystallised from ether (14.1g) mp 79-80°C. ^1H NMR (360MHz, CDCl_3) δ_{H} 1.24 (t, 3H,

-48-

$J=7.0\text{Hz}$, CH_2CH_3), 1.71 (2H, m, $\text{CH}_2\text{CH}_2\text{CH}_2\text{C}$), 2.32 (1H, m, $\text{CH}_2\text{CH}_2\text{CHHC}$), 2.68 (1H, m, $\text{CH}_2\text{CH}_2\text{CHHC}$), 3.36 (2H, m, $\text{CH}_2\text{CH}_2\text{CH}_2\text{C}$), 4.22 (2H, q, $J=7.0\text{Hz}$, CH_2CH_3), 6.26 (1H, bs, NH), 7.30 (5H, m, Ar H). m/z (CI^+) 248 ($\text{M}+1$)⁺.

5 c) (1) N-t-Butoxycarbonyl-3-phenyl-3-hydroxymethyl piperidine

3-Phenyl-3-ethoxycarbonyl piperidine 2-one (7.0g) was added portionwise to a stirred solution of lithium aluminium hydride (2.15g) in dry tetrahydrofuran (100ml). Once addition was complete the solution was warmed to reflux for two hours. The reaction was then cooled to room temperature, and water (3ml) and 1N sodium hydroxide solution (3ml) added, followed by t-butoxycarbonyl anhydride (6.17g) and dry dichloromethane (60ml). The resulting mixture was stirred at room temperature for 18 hours. The white precipitate was filtered off and the filtrate extracted into dichloromethane (250ml). The organic layers were dried (MgSO_4), filtered and the solvent removed under reduced pressure. Product recrystallised from EtOAc/nHex (13.1g). mp 101-104°C. ^1H NMR (360MHz, CDCl_3) δ_{H} 1.46 (9H, s, $\text{C}(\text{CH}_3)_3$), 2.00-4.00 (CH_2 envelope), 7.35 (5H, m, ArH); m/z (CI^+), 291 ($\text{M}+1$)⁺.

d) (±) 3-Phenyl-3-(3,5-bis(trifluoromethyl)benzyloxymethyl) piperidine tosylate

25 KHMDS (21ml x 0.5mol) was added to a stirred solution of (±) N-t-butoxycarbonyl-3-phenyl-3-hydroxymethyl piperidine (279mg) in dry tetrahydrofuran (10ml) at -78°C. The solution was warmed to room temperature over 30min and then re-cooled to -78°C. 3,5-Bis(trifluoromethyl) benzyl bromide (179µl) was then added and the solution allowed to warm to room temperature over 18 hours. The reaction mixture was poured into water (50ml), and extracted into ethyl acetate (50ml). The organic extract was stirred over magnesium sulphate, filtered, and the solvent removed under

-49-

reduced pressure, to afford a yellow oil. Chromatography on SiO₂ (20%, EtOAc/nHex) afforded a clear oil. Treatment of the recovered oil with a saturated solution of hydrogen chloride in ether afforded removal of the protecting group. The recovered salt was taken up in water (20ml), basified with 4N sodium hydroxide solution, and extracted into ethyl acetate (50ml). The organic layer was dried (MgSO₄), filtered, and the solvent removed under reduced pressure to afford a clear oil. The recovered product was treated with p-toluene sulphonic acid to afford the tosylate salt (189mg) mp 179-180°C. ¹H NMR (360MHz, DMSO-D₆) δ_H [Tosyl signals omitted for clarity] 1.63 (1H, m, CH₂CH₂CHH), 1.74 (1H, m, CH₂CH₂CHH), 1.96 (1H, m, CH₂CHHCH₂), 2.02 (1H, m, CH₂CHHCH₂), 3.00 (2H, m, CH₂CH₂CH₂), 3.52 (1H, d, J=10.0Hz, NCHH-C), 3.55 (1H, d, J=6.0Hz, CCHH-OCH₂Ar), 3.62 (1H, d, J=6.0Hz, CCHH-OCH₂Ar), 3.65 (1H, d, J=10.0Hz, NCHH-C), 4.53 (1H, d, J=8.0Hz, OCHHAr), 4.60 (1H, d, J=8.0Hz, OCHHAr), 7.32 (5H, m ArH), 7.48 (2H, s, C-CH-CCF₃ x 2), 7.77 (1H, s, CF₃C-CH-CCF₃). m/z (CI⁺) 418 (M+1)⁺. C₂₈H₂₉NO₄SF₆ requires C, 57.04; H, 4.95; N, 2.37. Found C, 56.86; H, 4.65; N, 2.26%.

EXAMPLE 18

4-Phenyl-4-[1-(3,5-Bistrifluoromethyl)phenyl]ethoxymethyl]piperidine hydrochloride

METHOD A

a) 1-(3,5-Bistrifluoromethyl)phenyl-1-ethanol

Sodium borohydride (2.2g) was added to a stirred solution of 3,5-bistrifluoromethyl acetophenone (15.0g) in dry methanol (100ml). The resulting solution was stirred for 1 hour at room temperature, and then reduced to dryness under reduced pressure. The solid

residue was partitioned between saturated ammonium chloride solution and ethyl acetate. The organic layer was separated and dried (MgSO_4), filtered, and the solvent removed under reduced pressure. Recovered product was recrystallised from pentane (12.6g) mp 71-72°C. ^1H NMR (360MHz, CDCl_3) δ 1.56 (3H, d, $J=7.0\text{Hz}$, $\text{CH}-\text{CH}_3$), 2.00 (1H, bs, OH), 5.05 (1H, q, $J=7.0\text{Hz}$, $\text{CH}-\text{CH}_3$), 7.8 (1H, $\text{CF}_3\text{C}-\text{CH}-\text{CCF}_3$), 7.89 (2H, $\text{C}-\text{CH}-\text{CCF}_3 \times 2$).

b) 1-[3,5-(Bistrifluoromethyl)phenyl]-1-bromoethane

1-(3,5-Bistrifluoromethyl)phenyl-1-ethanol (10g) was treated with phosphorous tribromide (3.75ml). After 1 hour the mixture was added to water and extracted with hexane. The organic solution was dried (Na_2SO_4) and filtered through silica gel to give, after evaporation of the solvent *in vacuo*, the title compound as a colourless liquid. ^1H NMR (360MHz, CDCl_3) δ 2.08 (3H, d, $J=7\text{Hz}$), 5.21 (1H, q, $J=7\text{Hz}$), 7.80 (1H, s) and 7.87 (2H, s).

c) 4-Phenyl-4-[1-(3,5-(bistrifluoromethyl)phenyl)ethoxymethyl]piperidine

The title compound was prepared by the method of Examples 1 and 2 using 1-(3,5-bistrifluoromethyl)phenyl-1-bromoethane. Mpt 86-89°C. ^1H NMR (360MHz, $\text{DMSO}-d_6$) δ 1.29 (1H, d, $J=6.4\text{Hz}$), 2.05 (2H, m), 2.31 (2H, m), 2.71 (2H, m), 3.17 (2H, m), 3.21 (1H, d, $J=9.2\text{Hz}$), 3.45 (1H, d, $J=9.2\text{Hz}$), 4.56 (1H, q, $J=6.4\text{Hz}$), 7.27 (1H, m), 7.38 (4H, m), 7.72 (2H, s) and 7.96 (1H, s). m/z (CI^+) ($\text{M}^+ + 1$). $\text{C}_{22}\text{H}_{23}\text{F}_6\text{NO} \cdot \text{HCl} \cdot 0.25\text{H}_2\text{O}$ requires C, 55.94; H, 5.23; N, 2.96. Found C, 55.89; H, 5.27; N, 3.10.

METHOD B

a) 1-^tButoxycarbonyl-4-phenyl-4-[3,5-bistrifluoromethylbenzoyloxymethyl]piperidine

5

1-(3-Dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride (897mg) was added to a stirred solution of 3,5-bistrifluoromethyl benzoic acid (292mg) and 4-dimethylamine pyridine (483mg) in dry DMF (20ml). The resulting solution was stirred for 30 min at room temperature at which time the compound of Example 1 part a) (1.0g) was added. The resulting solution was stirred at room temperature for 19 hrs. At this time the reaction was diluted with water (200ml) and extracted into ethyl acetate. The organic layers were separated, washed with water, brine, and dried over MgSO₄. Filtration and removal of solvent under reduced pressure afforded a yellow oil. Purification by MPLC (20% EtOAc/nHexane) afforded the product as a clear oil. ¹H NMR (360MHz, CDCl₃) δ 1.4 (9H, s, N-CO-CCCH₃), 1.95 (2H, m, NCH₂-CHH x 2), 2.3 (2H, m, NCH₂-CHH x 2), 3.03 (2H, m, NCHH-CH₂ x 2), 3.8 (2H, m, NCHH-CH₂ x 2), 4.35 (2H, s, CH₂O-CO), 7.0-7.2 (5H, m, ArH), 8.01 (1H, s, CF₃C-CH-CCF₃), 8.25 (2H, s, C-CH-CCF₃ x 2).

20

b) 1-^tButoxycarbonyl-4-phenyl-4-[1-(3,5-bistrifluoromethylphenyl)vinylloxymethyl]piperidine

25

TiCl₄ (1.06g) was added to cooled (0°C) stirred THF under a dry N₂ atmosphere. After the exotherm had subsided the solution was allowed to warm to room temperature and THEDA (1.69g) added followed 15 min later by freshly activated Zn dust (819mg). The resulting mixture was stirred for 30 min at room temperature at which point CH₂Br₂ (216μl) and the compound of part a) (716mg) were added. The reaction was allowed to proceed for 18 hrs at room temperature. After this time the reaction was quenched with

30

saturated K_2CO_3 (7ml) and diluted with Et_2O . The resulting black suspension was filtered through a plug of GIII Al_2O_3 , eluting with 1% Et_3N/Et_2O . The filtrate was dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The residual oil was
5 purified by MPLC (10% $EtOAc/nHex$) to afford the product (290mg).
 1H NMR (360MHz, $CDCl_3$) δ 1.2 (9H, s, $C(CH_3)_3$), 1.95 (2H, m, $NCH_2-CHH \times 2$), 2.38 (2H, m, $NCH_2CHH \times 2$), 3.05 (2H, m, $NCHH-CH_2 \times 2$), 3.8 (2H, s, CH_2O-), 3.95 (2H, m, $NCHH-CH_2 \times 2$), 4.21 (1H, d, $J = 1.0Hz$, $C=CHH$), 4.63 (1H, d, $J = 1.0Hz$, $C=CHH$), 7.1-7.3 (5H, m, ArH), 7.7 (1H, s, $CF_3-C-CH-CCF_3$), 7.76 (2H, s, $C-CH-CCF_3 \times 2$).
10

c) 4-Phenyl-4-[1-(3,5-(bistrifluoromethyl)phenyl)ethoxymethyl]piperidine

15 The product of part (b) (290mg) was hydrogenated over 5% RH/Al_2O_3 in ethyl acetate for 30 min at atmospheric pressure. The catalyst was filtered off and solvent removed. The residual oil was purified by MPLC (5% $EtOAc/nHexane$) followed by treatment with ether/ HCl to afford the title compound. Identical in all respects to
20 that of Example 18, Method A, part (c).

EXAMPLE 19

25 1-Methyl-4-phenyl-4-[3,5(bistrifluoromethyl)benzyloxymethyl]piperidine tosylate

Sodium cyanoborohydride (147mg) was added to a stirred suspension of the compound of Example 2 (533mg) and formaldehyde (175mg, 0.5ml x 37%) in dry methanol containing acetic acid (1.0ml).
30 The resulting solution was stirred for 18 hours at room temperature. After this time the solvent was removed under reduced pressure and the residual oil taken up in water and basified to pH 10. The aqueous solution was extracted into ethyl acetate, separated and dried

-53-

(MgSO₄). Filtration and removal of solvent gave a yellow oil. Chromatography on silica gel (5% MeOH/CH₂Cl₂) afforded a clear oil (473mg). The recovered oil was treated with a solution of p-toluene sulphonic acid monohydrate (207mg) to afford the salt.

5 Recrystallisation from ethyl acetate gave the title compound as a white powder (580mg). mp 89-91°C. ¹H NMR (360MHz, DMSO₆) δ 2.01 (2H, m, NCH₂CH₂), 2.55 (2H, m, NCH₂CH₂), 2.67 (3H, s, NCH₃), 2.67 (3H, s, NCH₃), 2.71 (2H, m, NCH₂CH₂), 3.37 (2H, s, CH₂OCH₂Ar), 4.56 (2H, s, CH₂OCH₂Ar), 7.30-7.48 (5H, m, ArH), 7.70
10 (2H, s, C-CH-CCF₃ x 2), 7.99 (1H, s, CF₃C-CH-CCF₃); MS CI⁺ 432 (M+1)⁺.

The following compounds were prepared analogously.

15

EXAMPLE 20

1-Isopropyl-4-phenyl-4-[3.5(bistrifluoromethyl)benzyloxymethyl] piperidine tosylate

20

mp 158-60°C. ¹H NMR (DMSO-d₆) 1.09 (6H, d, J = 11.0Hz, (CH₃)₂CH), 2.01 (2H, m, NCH₂CH₂), 2.51 (2H, m, NCH₂CH₂), 3.19 (1H, sept, J = 11.0Hz, (CH₃)₂CH), 3.37 (2H, s, CH₂OCH₂Ar), 4.57 (2H, s, CH₂OCH₂Ar), 7.36-7.45 (5H, m, ArH), 7.73 (2H, s, C-CH-CCF₃ x 2), 8.00 (1H, s, CF₃C-CH-CCF₃); MS CI⁺ 460 (M+1)⁺; C₃₁H₃₅NO₄SF₆
25 requires C, 58.95; H, 5.59; N, 2.22. Found C, 59.02; H, 5.66; N, 2.26%.

EXAMPLE 21

1-(2-Phenyl)ethyl-4-phenyl-4-[3.5(bistrifluoromethyl)benzyloxymethyl] piperidine tosylate

30

mp 166-167°C. ¹H NMR (360MHz, CDCl₃ free base) δ 2.10 (2H, m, NCH₂CH₂), 2.41 (4H, m, NCH₂CH₂ and Ph-CH₂CH₂), 2.55 (2H, m,

NCH₂CH₂), 2.93 (4H, m, PhCH₂CH₂), 3.51 (2H, s, CH₂OCH₂Ar), 4.42 (2H, s, CH₂OCH₂Ar), 7.00-7.40 (10H, m, ArH), 7.49 (2H, s, C-CH-CCF₃); MS CI⁺ 522 (M+1)⁺; C₃₆H₃₇NO₄SF₆ ½ H₂O. Requires C, 61.53; H, 5.45; N, 1.99; Found C, 61.92; H, 5.30; N, 1.99%.

5

EXAMPLE 22

1-Isobutyryl-4-phenyl-4-[(3,5 bistrifluoromethyl)benzyloxymethyl] piperidine tosylate

10

mp 159-62°C. ¹H NMR (360MHz, DMSO d₆) 0.95 (6H, d, J = 11.0Hz, (CH₃)₂, 2.2-2.5 (4H, brm, NCH₂CH₂ x 2), 2.6 (2H, m, NCH₂CH₂), 2.8 (2H, d, J = 7.0Hz, N-CH₂-CH), 3.31 (1H, brm, CH-(CH₃)₂), 3.39 (2H, s, CH₂OCH₂Ar), 3.42 (2H, m, NCH₂(H₂), 4.57 (2H, s, CH₂OCH₂Ar), 7.31-7.45 (5H, m, ArH), 7.72 (2H, s, C-CH-CCF₃ x 2), 7.99 (1H, s, CF₃C-CH-CCF₃); MS CI⁺ 474 (M+1)⁺; C₃₂H₃₇NO₄SF₆.H₂O requires C, 57.90; H, 5.92; N, 2.11; Found C, 57.62; H, 5.74; N, 1.83%.

15

EXAMPLE 23

1-Isovaleryl-4-phenyl-4-[(3,5 bistrifluoromethyl)benzyloxymethyl] piperidine tosylate

20

mp 141-142°C. ¹H NMR (360MHz, DMSO d₆) 0.64 (9H, s, (CCH₃)₃), 1.49 (3H, m, NCH₂-CHH and (CH₃)₃C-CH₂), 2.02 (3H, m, NCH₂-CHH and ((CH₃)₃C-CH₂CH₂), 2.49 (2H, m, NCH₂CH₂), 2.59 (2H, m, NCH₂), 3.36 (2H, s, CH₂OCH₂Ar), 4.57 (2H, s, CH₂OCH₂Ar), 7.36-7.42 (5H, m, ArH), 7.72 (2H, s, C-CH-CCF₃ x 2), 7.99 (1H, s, CF₃C-CH-CCF₃); MS CI⁺ 502 (M+1)⁺; C₃₄H₄₁NO₄SF₆ requires C, 60.61; H, 6.13; N, 2.48; Found C, 60.41; H, 5.84; N, 2.01%.

25

30

EXAMPLE 24

(±)-5-[4-[1-(3,5-Bistrifluoromethylphenyl)ethoxymethyl]-4-phenyl-piperidin-1-yl]-2,4-dihydro-[1,2,4]-triazol-3-one

5

Prepared from the compound of Example 18 by the method of Example 12; mp 86-88°C. ¹H NMR (360MHz, CDCl₃) δ 1.35 (3H, d, J=6.5Hz), 2.00-2.16 (2H, m), 2.21-2.46 (4H, m), 2.67-2.78 (2H, m), 3.27 (1H, d, J=9Hz), 3.37 (1H, d, J=9Hz), 3.39 (2H, s), 4.30 (1H, q, J=6.5Hz), 7.26-7.39 (5H, m), 7.52 (2H, s), 7.76 (1H, s); m/e CI⁺ 529 (M+1). Found: C, 57.15; H, 4.99; N, 10.51%. C₂₅H₂₆F₆N₄O₂ requires C, 56.82; H, 4.96; N, 10.60.

10

EXAMPLE 25

15

4-Phenyl-4-[(3-chloro-5-methyl)benzyloxymethyl]piperidine hydrochloride

20

Prepared following the procedure of Examples 1 and 2; mp 159-160°C. C₂₀H₂₄NOCl. HCl requires C, 65.57; H, 6.88; N, 3.82; Found C, 65.69; H, 6.91; N, 3.60%.

EXAMPLE 26

25

4-Phenyl-4-[(3-bromo-5-methyl)benzyloxymethyl]piperidine hydrochloride

30

Prepared following the procedures of Examples 1 and 2; mp 55-57°C. C₂₀H₂₄NOBr. HCl 0.4H₂O requires C, 57.47; H, 6.22; N, 3.35; Found C, 57.36; H, 6.10; N, 3.09%.

EXAMPLE 274-Phenyl-4-[(3-methyl-5-t-butyl)benzyloxymethyl]piperidine
hydrochloride

5

Prepared following the procedures of Examples 1 and 2;
mp 51-52°C. $C_{24}H_{33}NO \cdot HCl \cdot H_2O$ requires C, 71.00; H, 8.94; N, 3.45;
Found C, 71.22; H, 9.16; N, 3.48%.

10

EXAMPLE 28Methyl-2-[4-phenyl-4-(3,5-bis(trifluoromethyl)benzyloxymethyl)
piperidine]acetate hydrochloride

15

Potassium carbonate (3mg) was added to a stirred solution of
the compound of Example 2 (4.47g) and methyl bromoacetate (1.5g) in
dry dimethyl formamide (25ml). Stirred at room temperature for 18
hours. After this time the reaction was poured into water (100ml),
extracted into ethyl acetate (50ml), dried ($MgSO_4$), filtered and the
solvent removed under reduced pressure. Purification by flash
chromatography (SiO_2 , 30% EtOAc/nHg) followed by treatment with
ethereal HCl afforded the product as a white powder (2.23g), mp 63-
65°C. $C_{24}H_{25}NO_3F_6 \cdot HCl \cdot \frac{1}{2}H_2O$ requires C, 53.90; H, 5.10; N, 2.62;
Found C, 54.01; H, 5.24; N, 2.74%

20

25

EXAMPLE 29N-methyl-4-phenyl-4-[3,5-bis(trifluoromethyl)benzyloxymethyl]
piperidine methiodide

30

Excess methyl iodide was added to a solution of the compound
of Example 19 (80mg) in dry acetone. The solution was warmed to
reflux for 4 hours, cooled to room temperature and the solvent

-57-

removed under reduced pressure. Product recrystallised from isopropanol (109mg), mp 197-199°C. $C_{23}H_{24}NOF_6 \cdot H_2O$ requires C, 46.71; H, 4.77; N, 2.37; Found C, 46.64; H, 4.37; N, 2.31%.

5

EXAMPLE 30

4-[4-(3,5-Bistrifluoromethyl)benzyloxymethyl]-4-phenyl-1-(4H-[1,2,4]triazol-3-yl-methyl)piperidine dihydrochloride

10

Potassium carbonate (608mg) was added to a suspension of the compound of Example 2 (500mg) and N-formamido-2-chloromethyl acetamide (382mg) in dry dimethyl formamide. The solution was warmed to 60°C for 2 hours and then to 140°C for a further 1 hour. The reaction was cooled to room temperature, diluted with water and extracted into ethyl acetate. The organic layers were separated, washed with water, then brine, and dried ($MgSO_4$). Filtration and removal of solvent afforded a yellow oil. Purification by flash chromatography (SiO_2 10%, MeOH/DCM) followed by treatment with ethereal hydrogen chloride afforded the product as a white powder (200mg), mp 119-120°C. $C_{24}H_{24}N_4OF_6 \cdot 2HCl$ requires C, 50.44; H, 4.59; N, 9.81. Found C, 50.40; H, 4.62; N, 10.10%.

15

20

EXAMPLE 31

25

5-[4-(3-Methyl-5-t-butyl)benzyloxymethyl]-4-phenyl-piperidin-1-ylmethyl]-2,4-dihydro-[1,2,4]-triazol-3-one

Prepared analogously to Example 12 from the compound of Example 27; mp 144-145°C. MS CI^+ 448 (M+1)⁺.

EXAMPLE 32

2-[4-Phenyl-4-[3.5(bis(trifluoromethyl)benzyloxymethyl)-N-3-pyridyl methyl-N-methyl acetamide. Dihydrochloride

5

Prepared analogously to Example 28; mp 135-137°C.
 $C_{30}H_{31}N_3O_2F_6 \cdot 2HCl \cdot 2H_2O$ requires C, 52.48; H, 5.14; N, 6.12; Found C, 52.12; H, 5.29; N, 6.22%.

10

EXAMPLE 33

4-[[(3.5-Bis(trifluoromethyl)benzyloxymethyl)-1-(2-methyl-thiazol-5-yl-methyl)-4-phenyl piperidine dihydrochloride

15

Prepared analogously to Example 28; mp 110-113°C.
 $C_{26}H_{26}N_2OSF_6 \cdot 2HCl$ requires C, 51.92; H, 4.89; N, 4.66; Found C, 51.72; H, 4.64; N, 4.56%.

20

EXAMPLE 34

4-[[(3.5-Bis(trifluoromethyl)benzyloxymethyl)-1-[1.2.4]-oxadiazol-3-ylmethyl-4-phenyl piperidine hydrochloride

25

Prepared analogously to Example 28; mp 90-91°C.
 $C_{24}H_{23}N_3O_2F_6 \cdot HCl$ requires C, 53.79; H, 4.51; N, 7.84; Found C, 53.77; H, 4.52; N, 7.53%.

30

EXAMPLE 35

(±)5-[4-(3.5-bis(trifluoromethyl)benzyloxymethyl)-4-phenyl-piperidin-yl)-1-ethyl]-2.4-dihydro-[1.2.4]-triazol-3-one tosylate

Prepared analogously to Example 12; mp 230-231°C.
 $C_{32}H_{34}N_4O_5SF_6 \cdot \frac{1}{2}H_2O$ requires C, 54.16; H, 4.97; N, 7.89; Found C, 54.12; H, 4.74; N, 7.99%.

5

EXAMPLE 36

1-[4-(3,5-Bistrifluoromethyl)-benzyloxymethyl-4-phenyl-
piperidin-1-yl]-2-pyrrolidin-1-yl-acetamide

10

Prepared analogously to Example 10, mp 180-182°C.
 $C_{34}H_{36}N_2SO_5F_6$ requires C, 58.28; H, 5.47; N, 3.99; Found C, 58.45; H, 5.60; N, 3.92%.

EXAMPLE 37

15

N-methanesulphonyl-2-[4-phenyl-4-(3,5-bistrifluoromethyl)
benzyloxymethyl] piperidin-1-ylacetamide

(a) N-Bromoacetyl-methanesulfonamide

20

Sodium hydride (1.68g x 60%) was added to a stirred solution of methanesulfonamide (2.0g) in dry tetrahydrofuran (20ml) at room temperature. The resulting solution was stirred at room temperature for 1 hour, as which time it was treated with a solution of bromoacetyl bromide (4.2g) in dry tetrahydrofuran (10ml). After 1 hour the solvent was removed under reduced pressure and the residue taken up in water and acidified to pH3. The acidic solution was extracted into ethyl acetate, dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Recrystallisation from isopropanol afforded the product as white needles: mp 112-114°C.

25

30

(b) N-methanesulphonyl-2-[4-phenyl-4-(3,5-bistrifluoromethyl)
benzyloxymethyl] piperidin-1-ylacetamide

-60-

Prepared analogously to Example 28 from the product of part (a) and the compound of Example 2; mp 97-99°C.

$C_{24}H_{26}H_2SO_4F_6 \cdot \frac{1}{2}H_2O$ requires C, 51.33; H, 4.84; N, 4.99; Found C, 51.47; H, 4.83; N, 5.01.

5

EXAMPLE 38

N-phenylsulphonyl-2-[4-phenyl-4-(3,5-bis(trifluoromethyl)benzyloxymethyl)piperidin-1-yl]acetamide

10

(a) N-Bromoacetylphenylsulfonamide

Prepared analogously to the compound of Example 36, part (2).

(b) N-phenylsulphonyl-2-[4-phenyl-4-(3,5-bis(trifluoromethyl)benzyloxymethyl)piperidin-1-yl]acetamide

15

Prepared analogously to Example 37 from the product of part (a) and the compound of Example 2; mp 110-114°C. MS CI^+ 614 (M+1)⁺.

20

EXAMPLE 39

4-Phenyl-4-[(3-phenyl)benzyloxymethyl]piperidine hydrochloride

25

Prepared following the method of Examples 1 and 2. The crude concentrate was crystallised from hot ethyl acetate to yield the title compound as a white crystalline solid (2.60g); m.p. 158.5-159.0°C (EtOAc). 1H NMR (360MHz, d_6 -DMSO) 9.00 (2H, bs, $+NH_2$), 7.35-7.60 (12H, m), 7.26 (1H, t, J=7.2) and 7.16 (1H, d, J=7.6, Ar-H), 4.46 (2H, s, OCH_2Ar), 3.46 (2H, s, $C.CH_2O$), 3.16 (2H, m, 2 x $CHH.CH_2N$), 2.71 (2H, t, J=10.5, 2 x $CHH.CH_2N$), 2.34 (2H, bm) and 2.13 (2H, m, CH_2NCH_2). m/z (CI^+) 358 (M+1, 100%). Found C, 76.51; H, 7.44;

30

-61-

N,3.70. $C_{25}H_{27}NO.HCl$ requires C, 76.21; H, 6.92; N, 3.56%.
HPLC > 99.5%.

EXAMPLE 40

5

5-[4-(3-Phenyl)benzyloxymethyl]-4-phenyl-piperidin-1-ylmethyl-2,4-dihydro-[1,2,4]-triazol-3-one

10

Prepared from the compound of Example 39 (2.0g) as described in Example 12. Flash silica gel chromatography eluting with 9:1 dichloromethane:methanol ($R_f=0.21$) gave a yellow gloss (1.8g).

15

Crystallisation from ethyl acetate and diethyl ether gave the title compound as solids (1.56g); m.p. 148-149°C (EtOAc-Et₂O). ¹H NMR (360MHz, d₆-DMSO) 11.21 (1H, bs) and 11.16 (1H, s, 2 x NH), 7.29-7.59 (12H, m), 7.19 (1H, t, J=7.2) and 7.12 (1H, d, J=7.6, Ar-H), 4.41 (2H, s, OCH₂Ar), 3.43 (2H, s, C.CH₂O), 3.15 (2H, s, NCH₂. C=N), 2.55 (2H, bm, 2 x CHH.CH₂N), 2.15 (4H, bm) and 1.93 (2H, m, 2 x CHH.CH₂N). m/z (CI⁺) 455 (M+1, 100%). Found C, 74.02; H, 6.61; N, 12.47. $C_{28}H_{30}N_4O_2$ requires C, 73.97; H, 6.66; N, 12.32%.

20

HPLC > 99.5%.

EXAMPLE 41

25

5-[4-(4-Benzyloxymethyl)-4-phenyl-piperidin-1-ylmethyl]-2,4-dihydro-[1,2,4]-triazol-3-one hydrochloride

Prepared from the compound of Example 5 by the method of Example 12; m.p. 144-147°C. $C_{22}H_{26}N_4O_2.HCl$ requires C, 69.82; H, 6.93; N, 14.80; Found C, 69.78; H, 6.84; N, 14.64%.

EXAMPLE 42N-[2-Amino-2-methyl propionamidol-4-phenyl-4-
[3.5(bis(trifluoromethyl)benzyloxymethyl)piperidine hydrochloride

5

Prepared from the compound of Example 2 by the method of Example 9; m.p. 156-159°C. $C_{25}H_{28}N_2O_2F_6 \cdot HCl$ requires C, 55.71; H, 5.42; N, 5.19; Found C, 55.43; H, 5.40; N, 5.00%.

10

EXAMPLE 434-Phenyl-4-[3.5(bis(trifluoromethyl)benzyloxyethyl)piperidine
hydrochloride

15

a) 4-Acetyl-1-^tbutyloxycarbonyl-4-phenyl piperidine

4-Acetyl-4-phenyl piperidine (2.2g) and di-*tert*-butyldicarbonate (2.83g) were dissolved in dichloromethane and stirred for one hour. The solvent was removed and the residue was recrystallised from petrol to yield a white solid (2.6g). m/z (CI⁺), 303.

20

b) 1-^tButyloxycarbonyl-4-(1-hydroxyethyl)-4-phenyl piperidine

The ketone above (2.0g) was dissolved in methanol (20ml) and reacted with sodium borohydride (500mg). The reaction was stirred for one hour and the solvent was removed. The residue was purified by silica chromatography to yield a white solid (1.8g). m/z (CI⁺), 306 (M+1)⁺.

25

c) 4-Phenyl-4-[3.5(bis(trifluoromethyl)benzyloxyethyl)
piperidine hydrochloride

30

Prepared from the compound of part b) as described in Example 2; m.p. 209-211°C. $C_{22}H_{23}NOF_6 \cdot HCl$ requires C, 56.47; H, 5.17; N, 2.99; Found C, 56.64; H, 5.27; N, 2.91%.

EXAMPLE 44

4-(3,4-Dichlorophenyl)-4-[3,5-bis(trifluoromethyl)benzyloxy
methyl]piperidine hydrochloride

5

Prepared from 3,4-dichlorophenyl acetic acid by the method of Example 14; m.p. 174°C. $C_{21}H_{19}Cl_2F_6NO \cdot HCl$ requires C, 48.25; H, 3.86; N, 2.68. Found C, 48.32; H, 3.80; N, 2.46.

10

EXAMPLE 45

1-[4-(3,5-Bistrifluoromethylbenzyloxymethyl)-4-phenyl-
piperidin-1-yl]-2-pyridin-3-yl ethanone

15

Prepared from the compound of Example 2 by the method of Example 9; m.p. 155°C. $C_{28}H_{26}F_6N_2O_2 \cdot C_7H_8SO_3$ requires C, 59.31; H, 4.84; N, 3.95. Found C, 59.30; H, 4.71; N, 3.82.

EXAMPLE 46

20

1-[4-(3,5-Bistrifluoromethylbenzyloxymethyl)-4-phenyl-
piperidin-1-yl]-2-pyridin-2-yl ethanone tosylate

25

Prepared from the compound of Example 2 by the method of Example 9; m.p. 153°C. $C_{28}H_{26}F_6N_2O_2 \cdot C_7H_8SO_3 \cdot H_2O$ requires C, 57.85; H, 4.99; N, 3.85. Found C, 58.08; H, 4.85; N, 3.66.

EXAMPLE 47

30

1-[4-(3,5-Bistrifluoromethylbenzyloxymethyl)-4-phenyl-
piperidin-1-yl]-2-pyridin-4-yl ethanone

Prepared from the compound of Example 2 by the method of Example 9; m.p. 153°C. $C_{28}H_{26}F_6N_2O_2 \cdot C_7H_8SO_3 \cdot 0.25H_2O$ requires C, 58.94; H, 4.88; N, 3.93. Found C, 58.80; H, 4.83; N, 3.85.

5

EXAMPLE 48

1-[4-(3,5-Bistrifluoromethylbenzyloxymethyl)-4-phenyl-piperidin-1-yl]-3-dimethylamino-propan-1-one

10

Prepared from the compound of Example 2 by the method of Example 9; m.p. 133°C. $C_{26}H_{30}F_6N_2O_2 \cdot C_7H_8SO_3$ requires C, 57.55; H, 5.56; N, 4.07. Found C, 57.81; H, 5.81; N, 3.98.

15

EXAMPLE 49

2-[4-(3,5-Bistrifluoromethylbenzyloxymethyl)-4-phenyl-piperidin-1-yl]acetate sodium salt

20

Prepared from the compound of Example 2 by the method of Example 27; m.p. 183-185°C. $C_{23}H_{23}F_6NO_3 \cdot Na$ requires C, 55.42; H, 4.65; N, 2.81. Found C, 55.14; H, 4.56; N, 2.80.

EXAMPLE 50

25

4-[4-(3,5-Bistrifluoromethylbenzyloxymethyl)-4-phenyl-piperidin-1-yl]-butyrate sodium salt

30

Prepared from the compound of Example 2 by the method of Example 27; m.p. > 230°C. $C_{25}H_{26}F_6NO_3 \cdot Na \cdot 0.5H_2O$ requires C, 56.18; H, 5.09; N, 2.62. Found C, 55.96; H, 5.41; N, 2.49.

-65-

EXAMPLE 51

Methyl-4-[4-(3,5-bis(trifluoromethyl)benzyloxymethyl)-4-phenyl-piperidin-1-yl]-butyrate hydrochloride

Prepared from the compound of Example 2 by the method of Example 27; m.p. 103°C. $C_{26}H_{29}F_6NO_3 \cdot HCl$ requires C, 56.37; H, 5.46; N, 2.53. Found C, 56.13; H, 5.33; N, 2.54.

EXAMPLE 52

1-[4-(3,5-Bis(trifluoromethyl)benzyloxymethyl)-4-phenyl-piperidin-1-yl]-3-dimethylamino ethanone tosylate

Prepared from the compound of Example 2 by the method of Example 27; m.p. 186-188°C. $C_{25}H_{28}F_6N_2O_2 \cdot C_7H_8SO_3$ requires C, 56.97; H, 5.38; N, 4.15. Found C, 56.89; H, 5.45; N, 4.04.

EXAMPLE 53

1-[4-(3,5-Bis(trifluoromethyl)benzyloxymethyl)-4-phenyl-piperidin-1-yl]-3-dimethylamino-pent-1-one tosylate

Prepared from the compound of Example 2 by the method of Example 27; m.p. 130-131°C. $C_{27}H_{32}F_6N_2O_2 \cdot C_7H_8SO_3 \cdot 0.5H_2O$ requires C, 57.38; H, 5.81; N, 3.94. Found C, 57.26; H, 5.77; N, 4.17.

EXAMPLE 54

4-(3,5-Bis(trifluoromethyl)benzyloxymethyl)-1-[1-(4-toluenesulphonyl)-imidazole-2-yl]-methyl-4-phenyl piperidine

-66-

Prepared from the compound of Example 2 by the method of Example 18; m.p. 99-100°C. $C_{32}H_{31}F_6N_3O_3S$ requires C, 58.98; H, 4.80; N, 6.45. Found C, 59.28; H, 4.85; N, 6.32.

5

EXAMPLE 55

4-(3,5-Bistrifluoromethylbenzyloxymethyl)-1-(1H-imidazole-2-yl-methyl)-4-phenyl piperidine hydrochloride

10

Prepared from the compound of Example 2 by the method of Example 18; m.p. 171°C. m/z (CI⁺) 498.

EXAMPLE 56

15

5-[4-(1-[3-Bromophenyl]-ethoxymethyl)-4-phenyl-piperidin-1-ylmethyl]-2,4-dihydro-[1,2,4]-triazol-3-one

Prepared by the methods of Example 18 Method A and Example 12. m/z (CI⁺) 452 (M+1)⁺.

20

EXAMPLE 57

4-phenyl-4-(1-(3-Bromophenyl)-ethoxymethyl)-piperidine Hydrochloride

25

Prepared by the method of Example 18 Method A. m/z (CI⁺) 375 (M+1)⁺.

EXAMPLE 58

30

5-[4-(1-[3-Chlorophenyl]-ethoxymethyl)-4-phenyl-piperidin-1-ylmethyl]-2,4-dihydro-[1,2,4]-triazol-3-one

-67-

Prepared by the method of Example 18 Method A. m/z (CI⁺)
392 (M+1)⁺.

EXAMPLE 59

5

4-phenyl-4-[3-Iodobenzyloxymethyl]-piperidine

Prepared by the method of Examples 1 and 2. m/z (CI⁺) 408
(M+1)⁺.

10

EXAMPLE 60

5-[4-(3-Iodobenzyloxymethyl)-4-phenyl-piperidin-1-ylmethyl]-2,4-dihydro-[1,2,4]-triazol-3-one

15

Prepared by the method of Examples 1, 2 and 12. m/z (CI⁺)
505 (M+1)⁺.

EXAMPLE 61

20

4-phenyl-4-[3-Chlorobenzyloxymethyl]-piperidine
Hydrochloride

25

Prepared by the method of Examples 1 and 2. C₁₉H₂₂
NOCl.HCl requires C, 64.78; H, 6.58; , 3.98. Found C, 64.85; H,
6.62; N, 3.99%.

EXAMPLE 62

30

5-[4-(3-Chlorobenzyloxymethyl)-4-phenyl-piperidin-1-ylmethyl]-2,4-dihydro-[1,2,4]-triazol-3-one

-68-

Prepared by the method of Examples 1, 2 and 12.
 $C_{22}H_{25}N_4O_2Cl$ requires C, 64.00; H, 6.10; N, 13.57; Found C, 63.77;
H, 5.94; N, 13.32%.

5

EXAMPLE 63

1-[4-(3,5-Dimethoxybenzyloxymethyl)-4-phenyl-piperidin-1-yl]-2-(1H-indole-3-yl) Acetamide

10

Prepared by the method of Examples 1, 2 and 10. m/z (CI⁺)
499 (M+1)⁺.

EXAMPLE 64

15

4-[4-(3,5-Dimethoxybenzyloxymethyl)-4-phenyl-piperidin-1-yl]methyl-Quinoline

Prepared by the method of Examples 1, 2 and 19. m/z (CI⁺)
483 (M+1)⁺.

20

EXAMPLE 65

3-[2-[4-(3,5-Dimethoxybenzyloxymethyl)-4-phenyl-piperidin-1-yl]ethyl]-1H-indole

25

Prepared by the method of Examples 1, 2 and 10. m/z (CI⁺)
513 (M+1)⁺.

EXAMPLE 66

30

1-(4-[3,5-Dichlorophenyl]-ethoxymethyl)-4-phenyl-piperidin-1-yl)-2-pyrrolidin-acetamide Hydrochloride

Prepared by the method of Example 18 Method A and
Example 10. $C_{26}H_{32}N_2O_2Cl_2 \cdot HCl \cdot \frac{1}{2}H_2O$ requires C, 59.95; H, 6.56;
N, 5.38; Found C, 59.76; H, 6.68; N, 5.46%.

5

EXAMPLE 674-phenyl-4-[3-^t-Butylbenzyloxymethyl]-piperidine.

10

Prepared by the method of Examples 1 and 2. m/z (CI⁺) 338
(M+1)⁺.

EXAMPLE 684-phenyl-4-[3-Cyanobenzyloxymethyl]-piperidine.

15

Prepared by the method of Examples 1 and 2. m/z (CI⁺) 307
(M+1)⁺.

EXAMPLE 69

20

5-[4-(3-Cyanobenzyloxymethyl)-4-phenyl-piperidin-1-ylmethyl]-2,4-dihydro-[1,2,4]-triazol-3-one

25

Prepared by the method of Examples 1, 2 and 12. m/z (CI⁺)
404 (M+1)⁺.

EXAMPLE 70

30

4-phenyl-4-[4-Cyanobenzyloxymethyl]-piperidine
Hydrochloride

Prepared by the method of Example 1 and 2. m/z (CI⁺) 343
(M+1)⁺.

-70-

EXAMPLE 71

5-[4-(4-Cyanobenzyloxymethyl)-4-phenyl-piperidin-1-ylmethyll-2,4-dihydro-[1,2,4]-triazol-3-one

5

Prepared by the method of Examples 1, 2 and 12. m/z (CI⁺)
404 (M+1)⁺.

EXAMPLE 72

10

5-[4-(3-⁴Butylbenzyloxymethyl)-4-phenyl-piperidin-1-ylmethyll-2,4-dihydro-[1,2,4]-triazol-3-one

15

Prepared by the method of Examples 1, 2 and 12. m/z (CI⁺)
435 (M+1)⁺.

EXAMPLE 73

20

1-[4-(3,5-Dimethoxybenzyloxymethyl)-4-phenyl-piperidin-1-yl]-3-piperidin-4-yl-propionamide Hydrochloride

Prepared by the method of Examples 1, 2 and 10. m/z (CI⁺)
481 (M+1)⁺.

25

EXAMPLE 74

1-(4-[3,5-Dichlorobenzyloxymethyl]-4-phenyl-piperidin-1-yl)-2-pyrrolidine acetamide Hydrochloride

30

Prepared by the method of Examples 1, 2 and 10.
C₂₅H₃₀N₂O₂Cl₂.HCl.½H₂O requires C, 59.77; H, 6.32; N, 5.37;
Found C, 59.67; H, 6.42; N, 5.21%.

-71-

EXAMPLE 75

4-[3-Chloro-5-methoxybenzyloxymethyl]-4-phenyl-piperidine
Hydrochloride

5

Prepared by the method of Examples 1 and 2. mp 150-152°C.

EXAMPLE 76

10

5-[4-(3-Chloro-5-methoxybenzyloxymethyl)-4-phenyl-piperidin-1-ylmethyl]-2,4-dihydro-[1,2,4]-triazol-3-one

15

Prepared by the method of Examples 1, 2 and 12. mp 147-149°C.

EXAMPLE 77

20

4-[3,5-Bis(trifluoromethyl)benzyloxymethyl]-4-phenyl-1-(5-pyrollidineethyl)carbamate piperidine hydrochloride

a) 4-[3,5-Bis(trifluoromethyl)benzyloxymethyl]-1-(4-nitrophenyl)carbamate-4-phenylpiperidine

25

Triethylamine (2.2g) was added to a solution of 4-[3,5-bis(trifluoromethyl)benzyloxymethyl]-4-phenylpiperidine hydrochloride (5g) in dry dichloromethane, 85ml and stirred for 15 mins before 4-nitrophenylcarbamate (2.2g) was added. After 3 hrs the mixture was washed with water (x 3), dried (MgSO₄), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel eluting with 4:1 hexanes:ethyl acetate to give the title compound as a clear oil. MS CI⁺ (559, M⁺).

30

-72-

b) 4-[3,5-Bis(trifluoromethyl)benzyloxymethyl]-4-phenyl-1-(5-pyrrolidine ethyl)carbamate piperidine hydrochloride

The compound of part (a) (2.8g) and 1-(2-hydroxyethyl)pyrrolidine (.55g) were dissolved in dry tetrahydrofuran (15ml). Sodium hydride (210mg) was added. After stirring for two hours the solvent was removed *in vacuo* and the residue partitioned between ethyl acetate and water. The organic layer was dried (MgSO₄), filtered and concentrated *in vacuo*. Azeotroped with toluene (x 3). The residue was treated with ethereal HCl then triturated with diethyl ether to give the title compound. NMR (360MHz, DMSO) 1.81-1.93 (6H, m), 2.14-2.19 (2H, m), 3.05 (4H, broad), 3.40 (2H, s), 3.72 (2H, broad), 3.52 (4H, s), 4.33 (2H, s), 4.55 (2H, s), 7.22-7.44 (5H, m), 7.74 (2H, s), 7.94 (1H, s), 11.23 (broad, N·H₂).

EXAMPLE 78

5-[4-(3,5-Bismethylbenzyloxymethyl)-4-phenyl-piperidin-1-ylmethyl]-2,4-dihydro-[1,2,4]-triazol-3-one

Prepared as described in Examples 1, 2 and 12. mp 144-145°C.

25

EXAMPLE 79

(±)-5-[4-(1-(3-N,N-Dimethylphenyl)-ethoxymethyl)-4-phenyl-piperidin-1-ylmethyl]-2,4-dihydro-[1,2,4]-triazol-3-one

30

Prepared as described in Example 18 Method B and Example 12. m/z (CI)⁺ 435 (M+1)⁺.

-73-

EXAMPLE 80

4-Phenyl-4-[1-(3-Isopropoxy)benzyloxymethyl]piperidine
Hydrochloride

5

Prepared as described in Examples 1, 2 and Example 12.
 m/z (CI)⁺ 354 (M+1)⁺.

EXAMPLE 81

10

5-[4-(1-(3-Isopropoxyphenyl)-ethoxymethyl)-4-piperidin-1-
ylmethyl]-2,4-dihydro-[1,2,4] triazol-3-one

15

Prepared as described in Example 18 Method A and Example
12. m/z (CI)⁺ 451 (M+1)⁺.

EXAMPLE 82

20

4-Phenyl-4-(2-cyanobenzyloxymethyl)piperidine
Hydrochloride

Prepared as described in Examples 1 and 2. m/z (CI)⁺ 307
(M+1)⁺.

25

EXAMPLE 83

4-(4-Methoxyphenyl)-4-[(3,5-
bistrifluoromethyl)benzyloxymethyl]piperidine Hydrochloride

30

Prepared as described in Example 14. m/z (CI)⁺ 448 (M+1)⁺.

-74-

EXAMPLE 84

4-Phenyl-4-[(2-methoxy-5-bromo)benzyloxymethyl]piperidine
Hydrochloride

5

Prepared as described in Examples 1 and 2. m/z (CI)⁺ 390
(M+1)⁺.

EXAMPLE 85

10

4-Phenyl-4-[1-(3,6-dichlorophenyl)-ethoxymethyl]piperidine
Hydrochloride

15

Prepared as described in Example 18 Method A and Example
12. mp 120-128°C. m/z (CI)⁺ 364 (M+1)⁺.

EXAMPLE 86

20

4-Phenyl-4-[1-(2,3-dichlorophenyl)-ethoxymethyl]piperidine
Hydrochloride

Prepared as described in Example 18 Method A and Example
12. m/z (CI)⁺ 364 (M+1)⁺.

25

EXAMPLE 87

30

4-Phenyl-4-[2,3-(dimethoxy)benzyloxymethyl]piperidine
Hydrochloride

Prepared as described in Example 18 Method A and Example
12. m/z (CI)⁺ 439 (M+1)⁺.

-75-

EXAMPLE 88

5 5-[4-(3-Isopropoxy)benzyloxymethyl-4-phenyl-piperidin-1-ylmethyl]-2,4-dihydro-[1,2,4]-triazol-3-one

mp 140°C.

EXAMPLE 89

10 4-[3-(Trifluoromethoxy)benzyloxymethyl-4-phenyl-piperidine Hydrochloride

mp 129°C.

EXAMPLE 90

15 The compound of Example 56 (15mg) was resolved by HPLC (CHIRACEL OJ. 5% EtOH/hexane 40°C) to afford the single enantiomers:

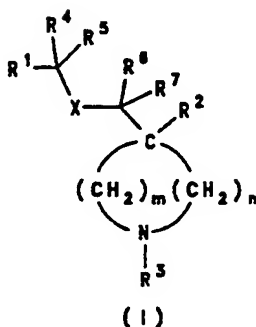
20 (+)5-[4-(1-[3-Bromophenyl]-ethoxymethyl)-4-phenyl-piperidin-1-ylmethyl]-2,4-dihydro-[1,2,4]-triazol-3-one. $[\alpha]^{23}_D = +23.8^\circ$ (6.0mg).

25 (-)5-[4-(1-[3-Bromophenyl]-ethoxymethyl)-4-phenyl-piperidin-1-ylmethyl]-2,4-dihydro-[1,2,4]-triazol-3-one. $[\alpha]^{23}_D = -24.2^\circ$ (8.2mg).

- 76 -

CLAIMS:

1. A compound of formula (I), or a salt or
 5 prodrug thereof:



15 wherein

m is 2, 3 or 4;

n is 0, 1 or 2 when m is 2 or 3, and n is 0 or
 1 when m is 4;

X represents O or S;

20 R¹ represents phenyl optionally substituted by
 1, 2 or 3 groups selected from C₁₋₆alkyl, C₂₋₆ alkenyl,
 C₂₋₆alkynyl, halo, cyano, nitro, trifluoromethyl,
 trimethylsilyl, -OR^a, SR^a, SOR^a, SO₂R^a, -NR^aR^b, -NR^aCOR^b,
 -NR^aCO₂R^b, -CO₂R^a or -CONR^aR^b, where R^a and R^b each
 25 independently represent H, C₁₋₆alkyl, phenyl or
 trifluoromethyl;

R² represents phenyl optionally substituted by
 1, 2 or 3 groups selected from C₁₋₆alkyl, C₂₋₆ alkenyl,
 C₂₋₆alkynyl, halo, cyano, nitro, trifluoromethyl,
 30 trimethylsilyl, -OR^a, SR^a, SOR^a, SO₂R^a, -NR^aR^b, -NR^aCOR^b,
 -NR^aCO₂R^b, -CO₂R^a or -CONR^aR^b, where R^a and R^b are as
 previously defined; heteroaryl selected from indazolyl,
 thienyl, furyl, pyridyl, thiazolyl, tetrazolyl and
 quinolyl; benzhydryl; or benzyl; wherein each heteroaryl

- 77 -

and each phenyl moiety of benzyl and benzhydryl may be substituted by C₁₋₆alkyl, C₁₋₆alkoxy, halo or trifluoromethyl; and

5 R³ represents H, COR⁹, CO₂R¹⁰, COCONR¹⁰R¹¹, COCO₂R¹⁰, SO₂R¹⁵, CONR¹⁰SO₂R¹⁵, C₁₋₆alkyl optionally substituted by a group selected from (CO₂R¹⁰, CONR¹⁰R¹¹, hydroxy, cyano, COR⁹, NR¹⁰R¹¹, C(NOH)NR¹⁰R¹¹, CONHphenyl(C₁₋₄alkyl), COCO₂R¹⁰, COCONR¹⁰R¹¹, SO₂R¹⁵, CONR¹⁰SO₂R¹⁵ and phenyl optionally substituted by one or
10 more substituents selected from C₁₋₆alkyl, C₁₋₆alkoxy, halo and trifluoromethyl), Y-R⁸ or CO-Z-(CH₂)_q-R¹²;

 R⁴, R⁵, R⁶ and R⁷ each independently represent H or C₁₋₆alkyl;

 R⁸ represents an optionally substituted
15 aromatic heterocycle;

 R⁹ represents H, C₁₋₆alkyl or phenyl;

 R¹⁰ and R¹¹ each independently represent H or C₁₋₆alkyl;

 R¹² represents NR¹³R¹⁴ or an optionally
20 substituted aromatic or non-aromatic azacyclic or azabicyclic group;

 R¹³ and R¹⁴ each independently represent H, C₁₋₆alkyl, phenyl optionally substituted by one or more of C₁₋₆alkyl, C₁₋₆alkoxy, halo or trifluoromethyl or
25 phenylC₁₋₄alkyl optionally substituted in the phenyl ring by one or more of C₁₋₆alkyl, C₁₋₆alkoxy, halo or trifluoromethyl;

 R¹⁵ represents C₁₋₆alkyl, trifluoromethyl or phenyl optionally substituted by one or more substituents
30 selected from C₁₋₆alkyl, C₁₋₆alkoxy, halo and trifluoromethyl;

 Y represents a hydrocarbon chain of 1, 2, 3 or 4 carbon atoms which may optionally be substituted by oxo;

 Z represents CH₂, O, S or NR¹⁰; and

- 78 -

q represents 0, 1, 2, 3, 4, 5 or 6.

5 2. A compound of formula (I) as claimed in claim 1 or a pharmaceutically acceptable salt thereof wherein X is 0, m is 2 and n is 2 and R² is phenyl or substituted phenyl.

10 3. A compound as claimed in any of claims 1 or 2 wherein R⁴, R⁶ and R⁷ are H.

 4. A compound as claimed in any of claims 1 to 3 wherein R⁵ is methyl.

15 5. A compound as claimed in any of claims 1 to 4 wherein R is substituted phenyl.

20 6. A compound as claimed in claim 5 wherein R¹ is phenyl optionally substituted in either or both the 3- and 5-positions by chloro, bromo, methyl, t-butyl, trifluoromethyl, methoxy, ethoxy, n- and isopropyl and n-, sec- and t-butyl.

25 7. A compound as claimed in any of claims 1 to 6 wherein R³ is H.

30 8. A compound as claimed in any of claims 1 to 6 wherein R³ is Y-R⁸ wherein Y is as defined in claim 1 and R⁸ is an oxazolyl, oxadiazolyl, imidazolyl, thiadiazolyl, triazolyl, pyrazinyl, pyridazinyl or triazinyl group substituted by methyl, methoxy, phenyl, oxo, thioxo, bromo, iodo, NH₂, SCH₃, COOH₂ or cyano group.

 9. A compound which is:

- 79 -

4-phenyl-4-[(3,5-bistrifluoromethyl)benzyloxy
methyl]piperidine;

2-[(3,5-bistrifluoromethyl)benzyloxymethyl]-2-
phenylpyrrolidine;

5 4-phenyl-4-[(2-trifluoromethyl)benzyloxymethyl]
piperidine;

4-phenyl-4-benzyloxymethylpiperidine;

4-phenyl-4-[(3-chloro-5-t-butyl)benzyloxymethyl]
piperidine;

10 4-phenyl-4-[(3,5-dichloro)benzyloxymethyl]piperidine;

4-phenyl-4-[(3-trifluoromethyl)benzyloxymethyl]
piperidine;

4-phenyl-4-[(4-trifluoromethyl)benzyloxymethyl]
piperidine;

15 1-acetyl-4-phenyl-4-[(3,5-bistrifluoromethyl)
benzyloxymethyl]piperidine;

1-methanesulphonyl-4-phenyl-4-[(3,5-bistrifluoromethyl)
benzyloxymethyl]piperidine;

20 5-[4-[(3,5-bistrifluoromethyl)benzyloxymethyl]-4-phenyl-
piperidin-1-ylmethyl]-2,4-dihydro[1,2,4]triazol-3-one;

2-[1'-imidazolyl]acetyl-4-phenyl-4-[(3,5-
bistrifluoromethyl)benzyloxymethyl]piperidine;

5-[4-[(3,5-bistrifluoromethyl)benzyloxymethyl]-4-(4-
fluorophenyl)-piperidin-1-ylmethyl]-2,4-

25 dihydro[1,2,4]triazol-3-one;

5-[4-[(3,5-bistrifluoromethyl)benzyloxymethyl]-4-(2-
fluorophenyl)-piperidin-1-yl)methyl]-2,4-
dihydro[1,2,4]triazol-3-one;

30 5-[4-[(3,5-bistrifluoromethyl)benzyloxymethyl]-4-(3-
fluorophenyl)-piperidin-1-yl)methyl]-2,4-
dihydro[1,2,4]triazol-3-one;

3-phenyl-3-[(3,5-bistrifluoromethyl)benzyloxymethyl]
piperidine);

- 80 -

- 4-phenyl-[4-[1-(3,5-bis(trifluoromethyl)phenyl)ethoxymethyl]piperidine;
1-methyl-4-phenyl-4-[3,5-bis(trifluoromethyl)benzyloxymethyl]piperidine;
5 1-isopropyl-4-phenyl-4-[3,5-bis(trifluoromethyl)benzyloxymethyl]piperidine;
1-(2-phenyl)ethyl-4-phenyl-4-[3,5-bis(trifluoromethyl)benzyloxymethyl]piperidine;
1-isobutyryl-4-phenyl-4-[3,5-bis(trifluoromethyl)benzyloxymethyl]piperidine;
10 1-isovaleryl-4-phenyl-4-[3,5-bis(trifluoromethyl)benzyloxymethyl]piperidine;
(±)-5-[4-[1-(3,5-bis(trifluoromethyl)phenyl)ethoxymethyl]-4-phenyl-piperidin-1-yl]-2,4-dihydro-
15 [1,2,4]triazol-3-one;
4-phenyl-4-[(3-chloro-5-methyl)benzyloxymethyl]piperidine;
4-phenyl-4-[(3-bromo-5-methyl)benzyloxymethyl]piperidine;
20 4-phenyl-4-[(3-methyl-5-t-butyl)benzyloxymethyl]piperidine;
methyl-2-[4-phenyl-4-(3,5-bis(trifluoromethyl)benzyloxymethyl)piperidine]acetate;
N-methyl-4-phenyl-4-[3,5-bis(trifluoromethyl)benzyloxymethyl]piperidine;
25 4-[3,5-bis(trifluoromethyl)benzyloxymethyl]-4-phenyl-1-(4H-[1,2,4]triazol-3-yl-methyl)piperidine;
5-[4-(3-methyl-5-t-butyl)benzyloxymethyl]4-phenylpiperidin-1-ylmethyl]2,4-dihydro-[1,2,4]triazol-3-one;
30 2-[4-phenyl-4-[3,5-bis(trifluoromethyl)benzyloxymethyl]-N-3-pyridylmethyl-N-methylacetamide;
4-[3,5-bis(trifluoromethyl)benzyloxymethyl]-1-(2-methylthiazol-5-ylmethyl)-4-phenylpiperidine;

- 81 -

4-[3,5-bis(trifluoromethyl)benzyloxymethyl]-1-
[1,2,4]oxadiazol-3-ylmethyl-4-phenylpiperidine;
(±)-5-[4-(3,5-bis(trifluoromethyl)benzyloxymethyl)-4-
phenylpiperidinyl-1-ethyl]-2,4-dihydro-[1,2,4]triazol-3-
one;

5

1-[4-(3,5-bis(trifluoromethyl)benzyloxymethyl)-4-
phenylpiperidin-1-yl]-2-pyrrolidin-1-ylacetamide;
N-methanesulphonyl-2-[4-phenyl-4-(3,5-
bis(trifluoromethyl)benzyloxymethyl)piperidin-1-
yl]acetamide;

10

N-phenylsulphonyl-2-[4-phenyl-4-(3,5-
bis(trifluoromethyl)benzyloxymethyl)piperidin-1-
yl]acetamide;

4-phenyl-4-[(3-phenyl)benzyloxymethyl]piperidine;

15

5-[4-(3-phenyl)benzyloxymethyl]-4-phenylpiperidin-1-
ylmethyl-2,4-dihydro-[1,2,4]triazol-3-one;

5-[(4-benzyloxymethyl)-4-phenyl-piperidin-1-ylmethyl]-
2,4-dihydro-[1,2,4]triazol-3-one;

N-[2-amino-2-methylpropionamido]-4-phenyl-4-[3,5-
bis(trifluoromethyl)benzyloxymethyl]piperidine;

20

4-phenyl-4-[3,5-bis(trifluoromethyl)benzyloxyethyl]
piperidine;

4-(3,4-dichlorophenyl)-4-[3,5-bis(trifluoromethyl)
benzyloxymethyl]piperidine;

25

1-[4-(3,5-bis(trifluoromethyl)benzyloxymethyl)-4-phenyl-
piperidin-1-yl]-2-pyridin-3-ylethanone;

1-[4-(3,5-bis(trifluoromethyl)benzyloxymethyl)-4-phenyl-
piperidin-1-yl]-2-pyridin-2-ylethanone;

1-[4-(3,5-bis(trifluoromethyl)benzyloxymethyl)-4-phenyl-
piperidin-1-yl]-2-pyridin-4-ylethanone;

30

1-[4-(3,5-bis(trifluoromethyl)benzyloxymethyl)-4-phenyl-
piperidin-1-yl]-3-dimethylamino-propan-1-one;

2-[4-(3,5-bis(trifluoromethyl)benzyloxymethyl)-4-phenyl-
piperidin-1-yl]acetate;

- 82 -

- 4-[4-(3,5-bis(trifluoromethyl)benzyloxymethyl)-4-phenyl-piperidin-1-yl]butyrate;
methyl-4-[4-(3,5-bis(trifluoromethyl)benzyloxymethyl)-4-phenyl-piperidin-1-yl]butyrate;
- 5 1-[4-(3,5-bis(trifluoromethyl)benzyloxymethyl)-4-phenyl-piperidin-1-yl]-3-dimethylaminoethanone;
1-[4-(3,5-bis(trifluoromethyl)benzyloxymethyl)-4-phenyl-piperidin-1-yl]-3-dimethylaminopent-1-one;
- 10 4-(3,5-bis(trifluoromethyl)benzyloxymethyl)-1-[1-(4-toluenesulphonyl)-imidazole-2-yl]methyl-4-phenylpiperidine;
- 4-(3,5-bis(trifluoromethyl)benzyloxymethyl)-1-(1H-imidazole-2-yl-methyl)-4-phenylpiperidine;
- 15 5-[4-(1-[3-bromophenyl]-ethoxymethyl)-4-phenyl-piperidin-1-ylmethyl]-2,4-dihydro-[1,2,4]-triazol-3-one;
- 4-phenyl-4-(1-(3-bromophenyl)-ethoxymethyl)-piperidine hydrochloride;
- 5-[4-(1-[3-chlorophenyl]-ethoxymethyl)-4-phenyl-piperidin-1-ylmethyl]-2,4-dihydro-[1,2,4]-triazol-3-one;
- 20 4-phenyl-4-[3-iodobenzyloxymethyl]-ethoxymethyl)-piperidine;
- 5-[4-(3-iodobenzyloxymethyl)-4-phenyl-piperidin-1-ylmethyl]-2,4-dihydro-[1,2,4]-triazol-3-one;
- 4-phenyl-4-[3-chlorobenzyloxymethyl]-piperidine hydrochloride;
- 25 5-[4-(3-chlorobenzyloxymethyl)-4-phenyl-piperidin-1-ylmethyl]-2,4-dihydro-[1,2,4]-triazol-3-one;
- 1-[4-(3,5-dimethoxybenzyloxymethyl)-4-phenyl-piperidin-1-yl]-2-(1H-indole-3-yl) acetamide;
- 30 4-[4-(3,5-dimethoxybenzyloxymethyl)-4-phenyl-piperidin-1-ylmethyl]-quinoline;
- 3-[2-[4-(3,5-dimethoxybenzyloxymethyl)-4-phenyl-piperidin-1-yl]ethyl]-1H-indole;

- 83 -

- 1-(4-[3,5-dichlorophenyl]-ethoxymethyl)-4-phenyl-piperidin-1-yl)-2-pyrrolidin-acetamide hydrochloride;
4-phenyl-4-[3-^t-butylbenzyloxymethyl]-piperidine;
4-phenyl-4-[3-cyanobenzyloxymethyl]-piperidine;
5 5-[4-(3-cyanobenzyloxymethyl)-4-phenyl-piperidin-1-ylmethyl]-2,4-dihydro-[1,2,4]-triazol-3-one;
4-phenyl-4-[4-cyanobenzyloxymethyl]-piperidine hydrochloride;
5-[4-(4-cyanobenzyloxymethyl)-4-phenyl-piperidin-1-ylmethyl]-2,4-dihydro-[1,2,4]-triazol-3-one;
10 5-[4-(3-^t-butylbenzyloxymethyl)-4-phenyl-piperidin-1-ylmethyl]-2,4-dihydro-[1,2,4]-triazol-3-one;
1-[4-(3,5-dimethoxybenzyloxymethyl)-4-phenyl-piperidin-1-yl]-3-piperidin-4-yl-propionamide hydrochloride;
15 1-(4-(3,5-dichlorobenzyloxymethyl)-4-phenyl-piperidin-1-yl)-2-pyrrolidine acetamide hydrochloride;
4-[3-chloro-5-methoxybenzyloxymethyl)-4-phenyl-piperidine hydrochloride;
5-[4-(3-chloro-5-methoxybenzyloxymethyl)-4-phenyl-piperidin-1-ylmethyl]-2,4-dihydro-[1,2,4]-triazol-3-one;
20 4-[3,5-bis(trifluoromethyl)benzyloxymethyl)-4-phenyl-1-(5-pyrrolodineethyl)carbamate piperidine hydrochloride;
5-[4-(3,5-bismethylbenzyloxymethyl)-4-phenyl-piperidin-1-ylmethyl]-2,4-dihydro-[1,2,4]-triazol-3-one;
25 (±)-5-[4-(1-(3-N,N-dimethylphenyl)-ethoxymethyl)-4-phenyl-piperidin-1-ylmethyl]-2,4-dihydro-[1,2,4]-triazol-3-one;
4-phenyl-4-[1-(3-isopropoxy)benzyloxymethyl]piperidine hydrochloride;
30 5-[4-(1-(3-isopropoxyphenyl)-ethoxymethyl)-4-phenyl-piperidin-1-ylmethyl]-2,4-dihydro-[1,2,4]-triazol-3-one;
4-phenyl-4-(2-cyanobenzyloxymethyl)piperidine hydrochloride;

- 84 -

4-(4-methoxyphenyl)-4-[(3,5-bis(trifluoromethyl)benzyloxymethyl)piperidine hydrochloride;
4-phenyl-4-[(2-methoxy-5-bromo)benzyloxymethyl)piperidine hydrochloride;
5 4-phenyl-4-[1-(3,6-dichlorophenyl)-ethoxymethyl)piperidine hydrochloride;
4-phenyl-4-[1-(2,3-dichlorophenyl)-ethoxymethyl)piperidine hydrochloride;
10 4-phenyl-4-[2,3-(dimethoxy)benzyloxymethyl)piperidine hydrochloride;
and salts thereof.

10. The use of a compound of the formula (I)
15 as defined in any of claims 1 to 9 or a pharmaceutically acceptable salt or a prodrug thereof in therapy.

11. The use of a compound of formula (I) as defined in any of claims 1 to 9 or a pharmaceutically acceptable salt thereof for use in the manufacture of a
20 medicament for the treatment of physiological disorders associated with any excess of tachykinins, especially substance P.

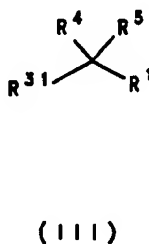
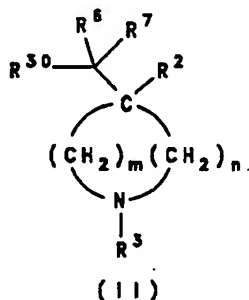
12. A pharmaceutical composition comprising a compound of the formula (I) as defined in any of claims 1 to 9 or a pharmaceutically acceptable salt thereof in association with a carrier thereof.

13. A method for the treatment or prevention of physiological disorders associated with an excess of tachykinins, especially substance P, which method comprises the administration to a patient in need thereof a tachykinin reducing amount of a compound of formula (I)

- 85 -

as defined in any of claims 1 to 9 or a pharmaceutically acceptable salt thereof or a pharmaceutical composition comprising a compound of the formula (I) as defined in any of claims 1 to 9 or a pharmaceutically acceptable salt thereof in association with a carrier therefor.

14. A process for the preparation of a compound as claimed in claim 1 which comprises reacting a compound of formula (II) with a compound of formula (III):



wherein R^1 , R^2 , R^4 , R^5 , R^6 , R^7 , m and n are as defined for formula (I), R^3 is as defined for formula (I) except that, when R^3 is H it is replaced by a suitable protecting group, such as $\text{CO}_2(\text{C}_{1-6}\text{alkyl})$; and one of R^{30} and R^{31} represents a leaving group and the other of R^{30} and R^{31} represents XH, where X is as defined for formula (I); in the presence of a base, followed by deprotection, if required.

15. A compound of the formula (I) as shown in claim (I) wherein R^1 , R^2 , R^3 , R^4 , R^5 , m and n are as defined in claim 1 and wherein R^6 and R^7 together with the carbon atom to which they are attached represent a $\text{C}=\text{C}(\text{R}^{41})(\text{R}^{51})$ group wherein R^{41} and R^{51} are independently hydrogen or alkyl or 1 to 5 carbon atoms.

INTERNATIONAL SEARCH REPORT

Inter national Application No
P B 93/02214

A. CLASSIFICATION OF SUBJECT MATTER

IPC 5 C07D401/06 C07D211/22 C07D211/20 C07D207/08 C07D413/06
C07D417/06 C07D521/00 A61K31/445

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 5 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 337 167 (DU PONT DE NEMOURS) 18 October 1989 see example 69 see page 2, line 14 - line 34 ---	1-3,5, 10-12
P,A	EP,A,0 522 808 (MERCK SHARP & DOHME) 13 January 1993 cited in the application see the whole document see page 7 - page 8 ---	1-12
P,A	J. AUTON. PHARMACOL. vol. 13, 1993 pages 23 - 93 C. A. MAGGI ET. AL. 'Tachykinin Receptors and Tachykinin Receptor Antagonists' cited in the application see the whole document -----	1-12

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- * 'A' document defining the general state of the art which is not considered to be of particular relevance
- * 'E' earlier document but published on or after the international filing date
- * 'L' document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- * 'O' document referring to an oral disclosure, use, exhibition or other means
- * 'P' document published prior to the international filing date but later than the priority date claimed

- * 'T' later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- * 'X' document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- * 'Y' document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- * 'A' document member of the same patent family

Date of the actual completion of the international search

7 February 1994

Date of mailing of the international search report

17. 02. 94

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2220 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax (+31-70) 340-3016

Authorized officer

Kissler, B

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
ALTHOUGH CLAIM 13 IS DIRECTED TO A METHOD OF TREATMENT OF (DIAGNOSTIC METHOD PRACTISED ON) THE HUMAN/ANIMAL BODY THE SEARCH HAS BEEN CARRIED OUT AND BASED ON THE ALLEGED EFFECTS OF THE COMPOUND/COMPOSITION.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter. Application No

P. B 93/02214

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0337167	18-10-89	AU-A- 3171789	28-09-89
		JP-A- 2049766	20-02-90
		US-A- 5086063	04-02-92
		US-A- 5019650	28-05-91

EP-A-0522808	13-01-93	AU-A- 2244092	11-02-93
		WO-A- 9301160	21-01-93
		WO-A- 9301159	21-01-93
		WO-A- 9301169	21-01-93
		WO-A- 9301165	21-01-93

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

☐ BLACK BORDERS

☐ IMAGE CUT OFF AT TOP, BOTTOM OR SIDES

☐ FADED TEXT OR DRAWING

☐ BLURRED OR ILLEGIBLE TEXT OR DRAWING

☐ SKEWED/SLANTED IMAGES

☐ COLOR OR BLACK AND WHITE PHOTOGRAPHS

☒ GRAY SCALE DOCUMENTS

☐ LINES OR MARKS ON ORIGINAL DOCUMENT

☐ REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY

☐ OTHER: _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.

THIS PAGE BLANK (USPTO)